Working group Herbicides (B) report

1. Need a risk assessment - Alopecurus, Lolium, Stellaria ,Papaver, Avena

2. Test methods

Good principle to characterise,
Add ALS to chemicals
Ideally use an ALS Target site population
Need more methodology details to understand causes of variation

Is there a coordination role in identifying and retaining standard populations

3. Availability of data

Where is clodinafop data
IPU/CTU explain
Good range

4. Proposed risk management

Agree high risk
Proposed strategy inadequate
Start again

5. Risk management strategy

Farm specific or field
Country specific
Principles common but implementation is not
List principles and how it will be disseminated
Refer to technical documentation

6. What to put on label

Where to find latest guidance,

There is a high risk of X weeds developing resistance to this product. It is essential that mitigation strategies are applied . Go to Y for details

Appendix 1

Product X (herbicide)

Background information

Product X is a herbicide for use in winter wheat, winter oats, winter rye and triticale. The mode of action is inhibition of acetolactate synthase (ALS) within target plants. There are many other herbicides already approved around the world with the same mode of action.

- The weeds which are the main target for this herbicide in the UK are:
    1. Broad-leaved weeds. Although populations of broad-leaved weeds resistant to ALS inhibitors are known around the world there are fewer incidents recorded in Europe. *Stellaria* and *Papaver* are the two main species where resistance has been confirmed in Europe. Both target site and metabolic mechanisms have been identified.
    2. Black-grass, *Alopecurus myosuroides*. A common pernicious weed found particularly on heavier soils. Resistance to a wide range of herbicide groups is known in Northern Europe. Two resistance mechanisms have been identified, target site resistance conferring strong resistance to ACCase inhibitors, and metabolic resistance, which gives weeds varying resistance to a wide range of herbicides. Target site resistance has also been confirmed to ALS inhibitors.

<u>Dossier for product X</u>

4. Resistance (Annex III. 6.3)

4.1 Background

<u>Proposed label text</u>
When herbicides with the same mode of action are used repeatedly over several years in the same field, selection of resistant biotypes can take place. These can propagate and may become dominating. A weed species is considered resistant to a herbicide if it survives a correctly-applied treatment at the recommended dose. Development of resistance in a weed species can be avoided or delayed by alternating (or tank-mixing) with suitable products having a different mode of action.

Resistance to crop protection chemicals is a common biological phenomenon that occurs in insects, fungi and weeds. It usually becomes evident after the repeated use of a particular pesticide selects for the naturally occurring resistant biotypes allowing them to multiply over several seasons until they become an obvious problem. Resistance to weeds arising from treatment with sulfonylurea herbicides was first detected in the US in 1987, five years after the first widespread commercial use of chlorsulfuron. Since that discovery, resistance to ALS inhibitors (sulfonylureas and imidazolinones) has been documented in 86 weed species.

4.2 Mechanisms of resistance to sulfonylureas

4.2.1 Target site resistance

This is the basis for the vast majority of the weed biotypes with ALS inhibitor resistance. A mutation in the gene encoding ALS renders the weed less sensitive to sulfonylureas.

4.2.2 Cross resistance

In general, a resistant biotype selected by one particular sulfonylurea is also resistant to other sulfonylureas. Where metabolic resistance is present, cross-resistance is usually evident to other chemical groups. However, some ALS inhibitor resistant dicot biotypes are controlled similarly to susceptible biotypes by herbicides with non-ALS inhibitor modes of action. This is an important factor in the agronomic management of resistant biotypes.

4.2.3 Metabolic resistance

Metabolic resistance is the main mechanism of resistance in *Alopecurus myosuroides.* Populations resistant to phenylureas (PUs) and ACCase inhibitors ('fops' and 'dims') have developed in many European countries. Such populations also exhibit decreased sensitivity to Product X.

4.3 Susceptibility levels of different A. myosuroides populations to Product X

Glasshouse work was undertaken to determine the base susceptibility to Product X of a range of populations of *A. myosuroides* with known resistance to other herbicides. A reference population with no resistance to either PUs or ACCase inhibitors was also included in the study. The following table contains the ED_{50} values (herbicide rate required to reduce fresh weight by 50% relative to the untreated) of the various populations for Product X, fenoxaprop and isoproturon.

Population	Product X g a.s./ha	Fenoxaprop g a.s./ha	Isoproturon g a.s./ha
Population 1 (Reference)	0.53	7.12	198
Population 2	7.67	17.59	498
Population 3	3.2	22.62	746
Population 4	1.34	18.95	237
Population 5	1.09	410.5	182
Population 6	2.71	48.8	218

Table 1: ED_{50} values of various *A.myosuroides* populations to Product X, fenoxaprop and isoproturon.

Population 1 (Reference) is a susceptible population that has been taken from an area which has historically never received a herbicide treatment. Population 2 is regarded as highly resistant to chlorotoluron while Population 5 and 6 are regarded as highly resistant to fenoxaprop. Populations 3 and 4 are known to have partial resistance to both chlorotoluron and fenoxaprop.

The large variability in control evident with fenoxaprop over the different populations is not as extreme with Product X. However the results demonstrate that cross resistance to Product X, probably due to enhanced metabolism of Product X is evident.

4.4 Risk of development and strategies for control of resistant weeds

Because of the short residual nature of Product X, we expect that it will only exert moderate selection pressure on sensitive weeds. These weeds can be controlled by other products with alternative modes of action. Furthermore as the weed spectrum of Product X is very different from other ALS inhibitors on the market, we expect that the selection pressure on the general weed population of European cereal crops will not be significantly increased. In contrast the commercialisation of Product X will bring a new mode of action for selective control of *Alopecurus myosuroides* at a time when development of resistance to current standards is a growing concern.

Because of the apparent high fitness of resistant biotypes it is imperative that strategies be implemented to minimise the risk of developing resistance and to manage it if it does occur. Practices which reduce selection pressure include rotating crops with rotating herbicide modes of action, using mixtures or sequential treatments

with different modes of action, using short residual herbicides and limiting the number of treatments per crop with the same mode of action for control of the same weed. These practices should be designed into an integrated weed control programme that incorporates cultural practices along with chemical methods, e.g. timely use of ploughing/cultivation, use of weed free seed and competitive crop stands and judicious use of non-selective herbicides.

As other sulfonylureas may be applied in sequence to Product X for the control of broad leaved weeds, it will be policy to recommend mixtures e.g. mecoprop, fluroxypyr where this occurs. Any incidences of poor control brought to our attention will be monitored.

Furthermore it is proposed to include a label statement to specifically highlight the control options available for the control of resistant *A. myosuroides.*

Proposed label text

Resistant *A. myosuroides:*

Where biotypes resistant to ureas (e.g. isoproturon, chlorotoluron) and/or ACCase inhibitors (‘fops’ and ‘dims’) are known to be present or where good resistance management practice is absent the following tank-mix or sequential options are recommended:

Product X applied in sequence with tri-allate, trifluralin or pendimethalin.

Product X applied in tank-mix with either trifluralin or pendimethalin.

Trials have shown that Product X applied as recommended above can give improved control of *A.myosuroides* in resistant situations. Glasshouse work has demonstrated the improved control of resistant *A.myosuroides* achieved by tank-mixing trifluralin with Product X.

The six previously mentioned populations (ref. section 4.3) were treated with Product X 10 g a.s./ha, trifluralin 960 g a.s./ha and a mixture of Product X 10 g a.s./ha plus trifluralin 960 g a.s./ha. Fenoxaprop-p-ethyl 55 g a.s./ha was applied for reference. Results of these tests are presented below.

	Product X	Fenoxaprop-p	Trifluralin	Product X + trifluralin
Population 1	94	83	0	98
Population 2	59	15	23	70
Population 3	74	18	3	86
Population 4	58	22	7	79
Population 5	81	13	7	84
Population 6	55	0	0	66

Table 2: % Reduction in *A.myosuroides* foliage weight of 6 resistant *A.myosuroides* populations following treatment with Product X, trifluralin, fenoxaprop-p-ethyl and a mixture of Product X plus trifluralin.

Product X gave superior control of all six populations compared to fenoxaprop-p-ethyl (range 55-94% compared to 0-83%). Trifluralin applied alone gave poor control of all populations (0-23%), however when applied in tank mixture with Product X, significantly improved control was observed over that achieved by Product X applied alone. On average over all six populations, control was increased from 70% with Product X to 81% with Product X + trifluralin.

Similar results were achieved by glasshouse work. Treatments were applied at the 1 leaf stage to 'Peldon' *A.myosuroides,* which is known to possess a high degree of metabolic resistance, and to a base population known to posses no resistance.

Treatments (g a.s./ha)	% Control 'Peldon' *A.myosuroides*	% Control Susceptible *A.myosuroides*
Product X 10	62	88
Product X 10 +trifluralin 960	68	94
Product X 10 + pendimethalin 2000	68	99
Trifluralin 960 (pre) followed by Product X 10 (post)	100	100
Pendimethalin 2000 (pre) followed by Product X (post)	64	100
Triallate 2250 (pre) followed by Product X 10 (post)	100	100

Table 3: % control of resistant and susceptible *A.myosuroides* from post emergence application assessed 19 DAT. (Mean 5 reps).

The addition of trifluralin or pendimethalin in tank mix with Product X gave improved control of both populations of *A.myosuroides*. However, sequential application of pre-emergence applied trifluralin or triallate, followed by post emergence application of Product X gave total control of both *A.myosuroides* populations.

Evaluation of product X

3.4 Resistance (IIIA 6.3)

Data relating to the occurrence and development of resistance or cross-resistance in populations of black-grass to 'Product X' were presented in the 'Resistance Addendum'.

3.4.1 Laboratory data/field information e.g. baseline monitoring

To date there have been several confirmed case of ALS inhibitor resistance in Europe (*Stellaria media, Papaver rhoeas and Alopecurus myosuroides*).

The activity of ‘Product X’ was evaluated on a range of resistant black-grass populations with known probable resistance mechanisms (see Table 3.4) via a long term project using the accepted methodology for glasshouse pot tests and simulated field tests using outdoor containers. A susceptible reference population with no resistance to either phenylureas (e.g. IPU, chlorotoluron) or ACCase inhibitors (aryloxyphenoxypropionates - ‘fops’and cyclohexanediones - ‘dims’) was included.

Full details of the materials and methods used in the studies were provided and were considered acceptable.

Table 3.4 : Summary of black-grass populations

Population	Mechanism	Resistance
1	n/a	No resistance to either phenyl-ureas or ACCase inhibitors
2	Enhanced metabolism	Highly resistant to both chlorotoluron & fenoxaprop
3	Similar to population 2	Highly resistance to both chlorotoluron & fenoxaprop
4	Low level enhanced metabolism	Partial resistance to both chlorotoluron & fenoxaprop
5	Target site + slight enhanced metabolism	Highly resistant to fenoxaprop
6	Target site & enhanced metabolism	Highly resistant to fenoxaprop

Base-line susceptibility of ‘Product X’ to the range of populations of black-grass with known resistance to other herbicides was established (see Table 3.5 below).

Table 3.5 : ED_{50} values of various black-grass populations to ‘Product X’, fenoxaprop and IPU

Population	Product X g a.s/ha	Fenoxaprop g a.s/ha	Isoproturon g a.s/ha
Population 1 (reference)	0.53 (1.0)	7.12 (1.0)	198 (1.0)
Population 2	7.67 (14.5)	17.59 (2.5)	498 (2.5)
Population 3	3.2 (6.0)	22.62 (3.2)	746 (3.8)
Population 4	1.34 (2.5)	18.95 (2.7)	237 (1.2)
Population 5	1.09 (2.1)	410.5 (57.6)	182 (0.9)
Population 6	2.71 (5.1)	48.8 (6.8)	218 (1.1)

Figures in brackets represent the ratio to the reference population i.e. resistance index

Using this accepted method for assessing resistance, ‘Product X’ was significantly less effective on three out of five standard resistant populations when compared with the standard susceptible population.

Initial results suggested that plants develop resistance to ‘Product X’ via enhanced metabolism, which renders the weed less sensitive, the population with the highest resistance due to enhanced metabolism showed the greatest degree of resistance to ‘Product X’. There was no evidence in the dossier to suggest that there is any ALS inhibitor target site resistance in black-grass.

Glasshouse pot tests were also used to establish that use of ‘Product X’ at reduced doses or against later growth stages would probably lead to lower levels of control, particularly in resistant or partially resistant crops.

Mixtures of ‘Product X’ with fenoxaprop, IPU and trifluralin were evaluated using glasshouse pot tests against the resistant populations of black-grass. Overall levels of control were improved when compared to each of the products used alone; however resistance was not overcome entirely depending on the degree and type of resistance. Simulated field studies confirmed that levels of control of highly resistant populations were not acceptable.

Further mixture and sequence options were evaluated using glasshouse pots tests and outdoor container tests. The most consistent results were obtained with mixtures of 'Product X' and clodinafop (the only treatment to give over 90% reduction of fresh weight of all populations). Based on this study, the most effective strategy for use against resistant populations would be tri-allate followed by 'Product X' in mixture with clodinafop; the most effective 'non-fop'option would be 'Product X' in mixture with pendimethalin. The applicant stated that the possible synergy between 'Product X' and pendimethalin (and possibly tri-allate) will be investigated further as this would be an effective sequence.

3.4.2 Resistance management strategy

In addition to the reference to follow the advice given in the Weed Resistance Action Group (WRAG) guidelines on combating grass weed resistance, the proposed label contains the following text:

'When herbicides with the same mode of action are used repeatedly over several years in the same field, selection of resistant biotypes can take place. These can propagate and may become dominating. A weed species is considered resistant to a herbicide if it survives a correctly-applied treatment at the recommended dose.
Development of resistance within a weed species can be avoided or delayed by alternating (or tank-mixing) with suitable products having a different mode of action.'

The applicant considers that 'Product X' will generally be used as part of a sequential or tank-mix spray programme, reducing the threat of resistance compared to other products that have activity over a wider range of species. Field work has confirmed the reliability and crop safety of a number of sequential and tank-mix options, however the applicant has a further programme of trials planned for 1996/97. In addition, the applicant stated that rotational broad-leaved crops tend to be treated with alternative graminicides with different modes of action, thus reducing the resistance risk further.

The applicant's management strategy is based on the following:

- inclusion of the WRAG statement on the product label
- to include tank-mix recommendations in commercial and advisory literature as soon as supporting data are available
- to apply for approval to put such tank-mix recommendations on the product label
- to ensure that all communication packages to customers include the latest information on the resistance situation and give advice on how best to use 'Product X' to reduce or prevent resistant black-grass occurring
- to monitor the status of resistance via long-term resistance management sites once commercial approval has been achieved

3.4.3 Assessment

It was considered acceptable that resistance studies were carried out using black-grass since black-grass is a major target of ‘Product X’ and has developed resistance to other herbicide groups. It is highly likely that black-grass represents the greatest resistance risk in the UK, however the proposed label includes a number of other weeds including chickweed and the base-line sensitivity of broad-leaved weeds must be considered.

The glasshouse pot tests confirmed that ‘Product X’ would show reduced control of resistant strains of black-grass when the mechanism of resistance was enhanced metabolism. Some mixtures showed higher levels of control of resistant or partially resistant populations. ‘Product X’ plus clodinafop gave the higher levels of control of resistant populations overall.

The glasshouse and simulated field studies demonstrated convincingly that ‘Product X’ can be affected by enhanced metabolism; however ‘Product X’ gave consistently high levels of control in a large number of field trials submitted to demonstrate control of black-grass.

The applicant considers that the use of ‘Product X’ in mixture with other active substances to expand the spectrum of weeds controlled (particularly grass weeds), will reduce the resistance risk. It is accepted that the use of graminicides with different modes of action in broad-leaved break crops following cereals may help to reduce the resistance risk. However, the continued development of other sulfonylurea herbicides for use in break crops must not be ruled out, thus increasing selection pressure for resistance.

The information provided was considered adequate to address the issue of resistance. The applicant has confirmed partial resistance of black-grass to ‘Product X’ and has proposed an acceptable and detailed resistance management strategy. The applicant has outlined the procedures for monitoring the resistance status and for the development of anti-resistance measures. The methods for disseminating any new information have also been addressed. The proposed label text is acceptable, having scope to be expanded as more information is confirmed e.g. advice for specific tank-mix recommendations.

Label Amendments

The standard black-grass resistance warning phrase must appear: ‘Strains of black-grass, chickweed and poppy have developed resistance to many black-grass herbicides, this may lead to poor control.’

Data requirements

i). Resistance to 'Product X' has been confirmed in a broad-leaved weed species (chickweed), therefore base-line sensitivity in broad-leaved species should be monitored.

HERBICIDE

Draft label for

PRODUCT X

- **Weed control**

Product X can be used on all varieties of winter wheat, winter oats, winter rye and triticale.

Maximum Individual Dose:	20 g/ha
Maximum Number of Treatments:	one per crop

Resistance Management Strategy

When herbicides with the same mode of action are used repeatedly over several years in the same field, selection of resistant biotypes can take place. These can propagate and may become dominating. A weed species is considered resistant to a herbicide if it survives a correctly-applied treatment at the recommended dose.

Development of resistance within a weed species can be avoided or delayed by alternating (or tank mixing) with suitable products having a different mode of action.

Note on resistant black-grass

The Weed resistance Action Group has produced Guidelines on avoiding and coping with resistant black-grass. Copies may be obtained from your distributor, crop adviser or product manufacturer.