Cyhoeddir yr atodiad hwn yn yr iaith y'i derbyniwyd gan Gynulliad Cenedlaethol Cymru.

Regulatory Evaluation of Herbicide Tolerant Maize (T25) Under Directive 90/220/EEC

Assessment of safety to human health and the environment

A paper by the ACRE Secretariat.

1. Background

This paper explains the health and environmental assessments for T25 GM maize that have been considered by ACRE during and since its approval for Part C marketing consent in Europe. It is intended to help inform a decision by the Agriculture Secretary of the National Assembly for Wales on whether it is appropriate to add CHARDON LL maize (a T25 variety) to the National List. The paper sets out the regulatory framework for GMOs, the safety evaluation of T25 and the implications of the proposed revisions to GMO risk assessment in Europe. The ACRE Secretariat and Chairman, Professor Alan Gray, will be happy to respond to any questions from the ARD Committee on 29 March.

1.1 The Deliberate Release Regulations

The release of genetically modified organisms (GMOs) is controlled in the UK by a framework of regulations* that aims to prevent or minimise damage to the environment from the escape or release of GMOs. Central to this framework is Directive 90/220/EEC, which provides a European Community-wide safety regime for the release and marketing of GMOs.
(* the framework is composed of the Genetically Modified Organisms (Deliberate Release) Regulations 1992 (amended), which give effect to Part VI of the Environmental Protection Act 1990. Together these implement Council Directive 90/220/EEC (and subsequent amendments) on the deliberate release into the environment of GMOs.)

The Regulations recognise two classes of release depending of the purpose; Part B releases for *research and development* and Part C releases for *placing on the market.* All applications for release consent require a detailed risk assessment of the proposed release and use of the GMO. This includes consideration not only of the potential damage to the environment but also any harm to human health and the safety of the GMO in animal feed. The risk assessment and supporting information is evaluated critically by experts on ACRE, and only if the risks are considered to be low will the Committee advise

that consent may be issued. No releases for research and development can take place in the UK without consent of the appropriate Ministers or if in Wales the Assembly Secretary acting jointly with MAFF. In issuing consent, the Ministers will also take account of safety issues raised by experts in other Government departments, the Statutory Nature Conservation Agencies and the general public.

1.1.a *Part C procedures for marketing GM crops*

As this paper focuses on the evaluation given to T25 maize in obtaining its Part C consent, a brief description of the Part C process might be helpful. Applications for Part C consent are submitted initially to any one of the 15 Member States (MS), which then reviews the application and forms an opinion. If that opinion is favourable, the lead MS (or Competent Authority (CA)) will forward the dossier to the Commission. The other 14 States then also evaluate the application in detail. If there are no objections the lead MS issues the marketing consent which applies throughout the European Community. If a MS (or more) is not happy then the Directive provides committee procedures for all MS to meet and resolve the issues. If this is not possible, it falls to the Council of Environment Ministers to decide.

Twelve GM plants already have Part C marketing approval in Europe. These include soya beans, oilseed rape, chicory, carnations and 3 types of GM maize - besides T25. The maize and soya are already imported in bulk into Europe for processing and use in animal feed.

1.2 T25 maize and its History in the European Regulatory Process

T25 is a genetically modified maize developed by AgrEvo (now Aventis) to be tolerant to the herbicide glufosinate ammonium. To make it tolerant the maize has inserted into it a new gene that makes the enzyme phosphinothricin acetyltransferase (PAT). PAT inactivates glufosinate herbicide inside the plant rendering it non-toxic. Unlike some GM plants, T25 does not contain functional antibiotic resistance marker genes.

T25 was submitted to the French Competent Authority in 1995. The scope of the application was to permit the growing of T25 in Europe and the importation of maize grain (grown mostly in North America) for processing into food and animal feed. The scope also permits the maize grown in Europe to be made into fodder and fed to farm animals. France evaluated the T25 dossier and concluded that the maize was safe for the environment, human health and as animal feed. The French CA therefore forwarded the T25 dossier to the Commission with a favourable opinion.

The UK and other Member States received the dossier from the Commission to conduct our own independent safety assessments. ACRE reviewed the application and issued advice on 20 June 1996. ACRE was satisfied that T25 did not pose a risk to human health and the environment. This included a consideration of animal feed safety in association with MAFF. The Advisory Committee on Novel Foods and Processes also considered the safety of T25 and advised that the product was safe for use in food*.
(*ACNFP's advice was published in the 1996 Annual Report)

On the strength of this body of expert advice, the UK informed the Commission on 25 July 1996 that we had no objection to T25 maize being placed on the European market. Member States voted in favour of marketing Consent on 18 March 1997, but France did not immediately issue the consent. It is understood that the delay was largely due to France at the time conducting a National debate on GM crops. Low risk GM crops like T25 maize, which are widely regarded as safe, emerged from the debate intact and France issued Part C consent on behalf of the European community in August 1998.

2. Safety Evaluation of T25 Maize under Directive 90/220/EEC

This section explains the risk assessment and safety evaluations conducted for T25 maize under the Directive. As stated above, no GMO can be placed on the Market without consent. The notification for Part C consent contains extensive information on the GM crop and its proposed use. The notifier must respond in detail to 50 prescribed questions* (www.env.detr.gov.uk/acre/index.htm). Together the answers to these questions build up a detailed dossier of information and data on which to conduct the risk assessment.
(*41 points under schedule 1 of the 1995 Regulations and 9 points under schedule 2 of the 1992 regulations)

In the UK, the risk assessment of T25 maize can be broken down into four main issues; Environment, human health, food safety and animal feed.

2.1 Environmental Safety

2.1.a *Potential for T25 maize to disseminate, establish and survive in the environment*

Maize has never become a weed in Europe or the United States although it is widely cultivated cereal, nor is there any historic evidence that it can compete with wild plants and invade natural habitats. In the agricultural environment, maize is dependent upon human intervention to ensure its survival. It is an annual plant that dies at the end of the season and can only propagate by seed. In cultivated maize its natural seed dispersal mechanism is non-functional*, and it has no sexually compatible wild relatives in Europe.
(*seeds are retained on the cob not shed onto the ground

Against this background, ACRE considered whether the introduction of the herbicide tolerance gene into T25 would enhance its capability to survive, establish and invade habitats. The Committee reviewed the behaviour of the T25 maize under field conditions and, in particular, data presented on morphological studies* and agronomic performance from field trials in the USA and Europe. These studies included experiments on, flowering time, plant height, yield, survival and persistence# and susceptibility to other approved herbicides. Laboratory studies on seed germination rates were also presented The experiments demonstrated that the T25 GM maize is indistinguishable from standard conventionally bred maize varieties. Further, like conventional maize T25 is extremely susceptible to cold and frost and can not survive the winter in the UK. The few volunteer maize plants that originate from dropped seed at harvest are easily controlled.

(*morphological studies consider the way a plant grows, its shape and form, and whether this is the same as the unmodified plant.)
(#incidence of volunteers in following crops)

ACRE agreed that based on numerous lines of evidence there is no indication that there had been any direct or indirect effect of the genetic modification on the ability of T25 to survive or out-compete wild plants. The T25 maize is no more likely to be invasive or weedy than non-GM maize varieties currently on the market.

2.1.b *Risk of transfer of herbicide tolerance trait to wild plants*

Transfer of genes between plants occurs via cross-pollination between sexually compatible individuals. In Europe, maize has no sexually compatible wild relatives. Therefore, ACRE reasonably concluded that the risk of gene escape to wild relatives is zero*.
(*the safety of T25 cross pollinating other maize crops is a food/feed issue – not an environmental concern)

2.1.c *Direct and indirect effects on non-target organisms*

Data was submitted on monitoring the susceptibility of T25 to a range of pests and diseases over three growing seasons in field trials. There were no differences in the susceptibility of T25 maize varieties compared with non-GM maize varieties and no evidence therefore that T25 was any more toxic or harmful to pests (and the beneficial creatures that eat the pests). Neither did T25 show any differences in susceptibility to diseases compared to non-GM maize.

2.2 Safety to Human Health

ACRE evaluated the risks to people who come directly or indirectly into contact with T25 maize or its pollen. Particular consideration was given to issues such as allergic reactions and possible toxicity. The food safety of T25 was assessed in detail by the ACNFP.

2.2.a *Safety of the genes inserted into T25 maize*

T25 maize contains the *pat* gene that makes the PAT enzyme needed to detoxify the herbicide glufosinate. Clearly maize does not normally make this enzyme and so risk assessment focussed initially on whether or not PAT is likely to cause allergic reactions or be toxic. The PAT enzyme is readily digested in human gastric fluids and is broken down quickly by heat and acids. These features make it very unlikely to be allergenic. The proteins in food and pollen that typically cause allergic reactions tend to be very stable and resistant to digestion, strong acids and heat. Well known allergens in peanuts and shellfish are good examples. PAT is not like this. Furthermore, the PAT enzyme protein sequence was compared to the sequences of thousands other proteins. None of the proteins with which PAT shared some similarity are know as allergens or toxins.

The biochemical properties of PAT were also considered. This enzyme has been well characterised biochemically and it is highly specific for its substrate (glufosinate herbicide). In tests, the PAT enzyme did not react with other closely related compounds. In conclusion, PAT is specific to inactivating glufosinate and is very unlikely to also interfere with other processes in T25 maize in unexpected ways or lead to unexpected toxins/allergens.

2.3 Food Safety

Food ingredents derived from T25 were approved in the UK in February 1997 following a full safety assessmnet by the ACNFP. A separate paper by the ACNFP Secretariat refers.

2.4 Animal Feed Safety

Livestock will be exposed to PAT protein when fed unprocessed grain or T25 maize leaves as silage. Experimental evidence indicates that the PAT protein is rapidly degraded in the digestive systems of pigs, chickens and cattle. The direct toxicity of PAT and any indirect effects of the genetic modification that might reduce the nutritional value of T25 maize were considered in the risk assessment.

2.4.a *Toxicity tests*

To assess the toxicity of the PAT protein, a repeated dose oral toxicity test on rats was carried out in which rat body weights, organ weight and food consumption were measured. These were unaffected in rats fed the T25 maize indicating that there was no evidence of mammalian toxicity. Studies later submitted by AgrEvo, on broiler chickens fed T25 maize also had no effect on growth performance and body composition supporting the rat studies but in an entirely different type of animal.

2.4.b *Composition and nutritional analyses*

Compositional analysis of silage and T25 maize grain showed that they are no different from other maize varieties in essential nutrients and anti-nutrients, and all measured values fell within the range reported for commercial maize varieties. Analyses included consideration of fatty acids and amino acids as well as phytic acid, which is a naturally occurring maize anti-nutrient. ACRE accepted that the T25 maize is no different from other conventionally bred maize.

2.4.c *Mycotoxins*

Infection of Maize kernels by fungi can produce toxins that are harmful to humans and animals eating infected maize. To ensure that the genetic modification had not unexpectedly increased susceptibility to fungi, field experiments were conducted. The results show that maize T25 was no more susceptible to infection than commercial maize varieties.

In conclusion, all of the evidence available to ACRE indicates that the genetic modification is very

specific and involves a non-toxic/non-allergenic gene product (PAT enzyme). The genetic modification of maize that resulted in T25 has no direct or indirect impact on the nutrient content or wholesomeness of the maize.

2.5 Further Research and Risk Assessment since Part C Consent was Issued for T25

There is an ongoing duty of care with all Part C consents that the consent holders and the regulatory authorities keep abreast of developments in science and evaluate these, were relevant, against the safety of approved GM products. If new scientific research gave justifiable reasons to believe that an approved GMO constitutes a risk to human health and the environment then Member States may take action to restrict or prohibit its use.

Research published since the 1996 evaluation of T25 indicates that GM maize lines containing the Bt gene to make them insect resistant might have non-target effects on insects such as lacewings and monarch butterflies. ACRE has evaluated each of these cases and concluded that they have no impact on the safety of GM maize lines that, like T25 herbicide tolerant maize, do not contain the Bt insecticidal gene. Likewise, a recent issue about the Cauliflower Mosaic virus (CaMV) promoter* was considered in detail by ACRE. The Committee advised that the CaMV promoter is safe and the risk assessments of approved products are unchanged.
(*the CaMV promoter is a small stretch of DNA used in most GM plants to switch on the inserted gene or genes)

There has been no new scientific evidence published since T25 was approved that would indicate the original risk assessment was wrong.

3. Changes in Risk Assessment and Monitoring of GMO Releases in Europe: Revision of Directive 90/220/EEC

Directive 90/220 has been in operation for several years and is currently under review based on a text put forward by the Commission in February 1998. Common position on the revised text was reached in December 1999 and is currently undergoing its second reading in the European Parliament. The main elements of the proposed changes to the Directive include *clarification* of risk assessment procedures, post market monitoring, time limited consents and a tough new labelling regime. The revisions will respond to public concerns about protection of human health and the environment and also provide a more transparent and predictable system for industry.

In the process of revising the Directive there has been good progress in setting out a clear framework for risk assessment of GMOs, and on requirements for post-market monitoring. Monitoring is considered to be extremely important in building confidence in the safety of a GMO and in verification of the risk assessment. Monitoring will also help to identify any unanticipated effects as early as possible. European Environment Ministers agreed in December 1998 that we should not wait until the new Directive is agreed to benefit from this progress. They therefore asked Member States to start making use of it immediately. To aid applicants, ACRE published Guidance on the risk assessment and

monitoring requirements (www.env.detr.gov.uk/acre/index.htm).

3.1 Do the Changes Effect the Safety Evaluation T25 Maize?

This new guidance makes little or no practical difference to the risk assessment procedures already practised in the UK. The harmonisation and clarification of risk assessment* adopted by Environment Minister simply brings many other Member States into line with the UK; indeed UK Government scientists and ACRE have been pivotal in guiding the revisions. It follows therefore that if T25 maize came forward for Part C approval again today, the risk assessment procedure in the UK would be to the same standard and rigour as was applied in 1996.

It has been suggested that the revisions to the Directive have introduced major changes to risk assessment since T25 maize was approved. As discussed above, this is not so – in the UK at least. It has further been suggested that the farm scale evaluations (see annex for background) raise new issues about the safety of T25 maize that were not considered in 1996. This is also not correct. The indirect effects of GMOs has always been part of the assessment, but the purpose of the farm scale evaluations is to test the effect on farmland biodiversity of *changes in management practices* associated with the use of herbicide tolerant crops. This is *not* a GM issue and it is irrelevant whether the crop is GM or not. In fact there are several herbicide tolerant crops under development that are not GM and have been produced by conventional plant breeding. The same biodiversity issues apply to these.

ACRE is entirely satisfied that the GM crops used in the evaluations are *themselves* no more hazardous to human health and the environment than are conventionally bred crops with similar traits. This is particularly so with T25 maize (no wild relatives, no antibiotic resistance genes etc) and its safety has been assessed exhaustively in the Part C notification under Directive 90/220/EEC.

The Environment Ministers decision of December 1998, in addition to risk assessment, attaches great importance to post market monitoring of GM crops. The farm scale evaluations are consistent with these requirements in so far as they provide a mechanism to monitor the use of the approved product post marketing approval. Post market monitoring is also an effective way to evaluate issues such long term feeding and possible delayed effects on animal health.

In conclusion, if the application for T25 came forward today, ACRE's advice would be unchanged. Under Directive 90/220 and the terms of the proposed revisions, T25 is considered to be safe for human health, the environment and for use in animal feed. ACRE has however advise differently in one respect, namely that there are biodiversity issues surrounding the new use of the herbicide. But consistent with post market monitoring requirements ACRE is confident that the farm scale evaluations will address the issue. We can be confident also that if the evaluations do reveal an unacceptable impact of the herbicide on biodiversity then herbicide approval *will not be given* under the pesticide regulations. If the evaluations did reveal an unexpected GM specific risk then the Directive permits immediate suspension

of Part C marketing consent. It is reasonable to conclude therefore that all appropriate measures *have been taken* to protect human health and the environment.

The analysis above using T25 as an example shows how the inter-linking regulatory regimes are intended to function in practice. Regulatory approvals are not denied under one set of regulations where the issues are dealt with elsewhere in the regulatory regime. Products are given incrementally each of the necessary approvals within a system that is designed to ensure appropriate protection for health and the environment while seeking to avoid regulatory gridlock.

Annex

Extract from ACRE's Annual Report 1999 Concerning the Farm Scale Evaluations and the Rationale Behind this Initiative.

The Farm Scale Evaluations Programme

We have been frequent advisors on the concept of farm scale evaluations of GM crops and have supported the initiative from its inception. Indeed an ACRE member, Professor Christopher Pollock, is Chairman of the farm scale evaluations scientific steering committee. The purpose of the current programme of evaluations is to test the effect on farmland biodiversity of changes in management practice associated with the use of herbicide tolerant oilseed rape and maize. The agreement reached between the Government and SCIMAC (Supply Chain Initiative on Modified Agricultural Crops) in November of this year foresaw the possibility of also including herbicide tolerant GM beet in the trials.

The argument in favour of farm scale evaluations has been stated many times but it is worth repeating here. The concern about herbicide tolerant crops is that they may allow farmers to produce fields with fewer weeds. Fewer weeds might mean fewer seeds and farmland invertebrates, which could have knock-on effects up the food chain leading to an overall reduction in farmland biodiversity. The only way to test this concern rigorously, within a proper scientific framework, is to grow the herbicide tolerant crops on a field scale in real fields with intensive ecological monitoring of key biodiversity indicator species.

We are satisfied that the GM crops used in the evaluations are themselves no more hazardous to human health and the environment than are conventionally bred crops with similar traits. This has been assessed thoroughly in the marketing applications submitted to the European Community under Directive 90/220/EEC.