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OECD Environment, Health and Safety Publications

Series on Harmonization of Regulatory Oversight in Biotechnology

No. 25

Module II: Herbicide Biochemistry, Herbicide Metabolism and the Residues in Glufosinate-Ammonium (Phosphinothricin)-Tolerant Transgenic Plants

Environment Directorate

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FOREWORD

The OECD's Working[1] Group on Harmonization of Regulatory Oversight in Biotechnology decided at its first session, in June 1995, to focus its work on the development of ***consensus documents*** which are mutually acceptable among Member countries. These consensus documents contain information for use during the regulatory assessment of a particular product. In the area of plant biosafety, consensus documents are being published on the biology of certain plant species, on selected traits that may be introduced into plant species, and on biosafety issues arising from certain general types of modifications made to plants.

This document, which was prepared by Germany as the lead country, addresses glufosinate-ammonium (phosphinothricin) metabolites and residues in genetically modified glufosinate-tolerant plants. It complements the *Consensus Document on General Information Concerning the Genes and Their Enzymes that Confer Tolerance to Phosphinothricin (Glufosinate-Ammonium) Herbicide (OECD Environmental Health and Safety Publications, Series on Harmonization of Regulatory Oversight in Biotechnology No.11)* as an additional module. It has been revised based on comments received from OECD Member countries and on subsequent comments from National Co-ordinators.

[1] In August 1998, following a decision by OECD Council to rationalise the names of Committees and Working Groups across the OECD, the name of the "Expert Group on Harmonization of Regulatory Oversight in Biotechnology" became the "Working Group on Harmonization of Regulatory Oversight in Biotechnology."

TABLE OF CONTENTS

PREAMBLE

OECD Member countries are now commercialising and marketing agricultural and industrial products of modern biotechnology. They have identified the need for harmonization of regulatory approaches for the assessment of these products, in order to avoid unnecessary trade barriers.

In 1993, **Commercialisation of Agricultural Products Derived through Modern Biotechnology** was instituted as a joint project of the OECD's Environment Policy Committee and its Committee on Agriculture. The objective of this project is to assist countries in their regulatory oversight of agricultural products derived through modern biotechnology – specifically in their efforts to ensure safety, to make oversight policies more transparent and efficient, and to facilitate trade. The project is focused on the review of national policies, with respect to regulatory oversight, that will affect the movement of these products into the marketplace.

The first step of this project was to carry out a survey concentrating on national policies in regard to regulatory oversight of these products. Data requirements for products produced through modern biotechnology, and mechanisms for data assessment, were also surveyed. The results were published in *Commercialisation of Agricultural Products Derived through Modern Biotechnology: Survey Results* (OECD, 1995).

Subsequently, an OECD Workshop was held in June 1994 in Washington, D.C. with the aim of improving awareness and understanding of the various systems of regulatory oversight developed for agricultural products of biotechnology; identifying similarities and differences in various approaches; and identifying the most appropriate role for the OECD in further work towards harmonization of these approaches. Approximately 80 experts in the areas of environmental biosafety, novel food safety and varietal seed certification, representing 16 OECD countries, eight non-member countries, the European Commission and several international organisations, participated in the Workshop. *Report of the OECD Workshop on the Commercialisation of Agricultural Products Derived through Modern Biotechnology* was also published by the OECD in 1995.

As a next step towards harmonization, the Working Group on Harmonization of Regulatory Oversight in Biotechnology instituted the development of Consensus Documents that are mutually acceptable among Member countries. The purpose of these documents is to describe common elements in the safety assessment of a new plant variety developed through modern biotechnology, to encourage information sharing and prevent duplication of effort among countries. These common elements fall into three general categories: the biology of the host plant species, or crop; the introduced genes and gene products conferring the novel trait; and biosafety issues arising from the introduction of certain general trait types into plants.

This Consensus Document is a "snapshot" of current information that may be relevant in a regulatory risk assessment. It is meant to be useful not only to regulatory officials, as a general guide and reference source, but also to industry and others carrying out research and product development.

It is anticipated that the Consensus Documents related to genes and products that confer novel traits, together with the relevant Consensus Documents on plant species biology and those providing information on biosafety issues arising from the use of general trait types in plants, will be of use in the biosafety assessment of genetically modified plants.

Reference to two other OECD publications that have appeared in recent years will also prove useful. *Traditional Crop Breeding Practices: An Historical Review to Serve as a Baseline for Assessing the Role of Modern Biotechnology* presents information concerning 17 different crop plants. It includes sections on phytosanitary considerations in the movement of germplasm and on current end uses of the crop plants. There is also a detailed section on current breeding practices. *Safety Considerations for Biotechnology: Scale-Up of Crop Plants* provides a background on plant breeding, discusses scale dependency effects, and identifies various safety issues related to the release of plants with "novel traits".[2]

2. For more information on these and other OECD publications, contact the OECD Publications Service, 2 rue André-Pascal, 75775 Paris Cedex 16, France. Fax: (33) 01.49.10.42.76; E-mail: PUBSINQ@oecd.org; or consult **http://www.oecd.org**

   Also see the BioTrack Online web page at **http://www.oecd.org/ehs/service.htm**

SUMMARY NOTE

This document summarises the information available on the herbicide biochemistry, the herbicide metabolism and the residues in glufosinate-ammonium (phosphinothricin)-tolerant transgenic plants.

Scope of this document: This document is limited to a condensed discussion of the herbicide biochemistry and metabolism specifically in glufosinate-ammonium (phosphinothricin)-tolerant transgenic plants. It is not intended to be an encyclopaedic review of all scientific experimentation with glufosinate tolerant plants or with the herbicide glufosinate itself. Especially, this document is not to be confused with the type of dossier currently composed for plant pesticides according to directive 91/414/EEC. Moreover, it does not discuss the plentiful information available on the use of the herbicide in agricultural and other applications. Food safety aspects of the use of glufosinate-ammonium on glufosinate-ammonium-tolerant plants are beyond the scope of this document. Such information is available from other sources, including the respective governmental organisations regulating herbicide use.

Section I - Biochemistry and Physiology of the Herbicide in Non-Tolerant and in Genetically Modified Glufosinate (Phosphinothricin)-Tolerant Plants

Glufosinate (phosphinothricin; DL-homoalanin-4-yl(methyl)phosphinic acid) is a racemic phosphinico amino acid (Hoerlein, 1994). Its ammonium salt (glufosinate-ammonium) is widely used as a non-selective herbicide and is the active ingredient of the commercial herbicide formulations Basta®, Buster®, Challenge®, Conquest®, Dash®, Final®, Finale®, Liberty® and Ignite®. The L-isomer of glufosinate is a structural analogue of glutamate and, therefore, is a competitive inhibitor of the enzyme glutamine synthetase (GS) of bacteria and plants (Bayer et al., 1972; Leason et al., 1982). The D-isomer is not a GS inhibitor and is not herbicidally active.

Due to the inhibition of GS, non-tolerant plant cells accumulate large amounts of toxic ammonia produced by nitrate assimilation and photorespiration (Tachibana et al., 1986) and the level of available glutamine drops (Sauer et al., 1987). Damage of cell membranes and inhibition of photosynthesis are followed by plant cell death. The action of glufosinate is dependent on environmental conditions. Temperatures below 10°C, as well as drought stress, reduce its efficacy because of the limited metabolic activity of the plant (Donn, 1982). Also, light is an important factor for the action of glufosinate (Koecher, 1983).

In genetically modified glufosinate-tolerant plants, the L-isomer of glufosinate is rapidly metabolized by the action of the enzyme phosphinothricin acetyltransferase (PAT) into the non-phytotoxic stable metabolite N-acetyl-L-glufosinate (2-acetamido-4-methylphosphinico-butanoic acid). N-acetyl-L-glufosinate does not inhibit glutamine synthetase. Therefore, no phytotoxic physiological effects are observed in genetically modified glufosinate-tolerant plants.

Glufosinate is a contact herbicide and is taken up by the plant primarily through the leaves (Haas and Müller, 1986). There is no uptake from the soil through the roots, presumably because of the rapid degradation of glufosinate by soil microorganisms. There is limited translocation of glufosinate within the plant. After application of L-glufosinate, N-acetyl-L-glufosinate and further metabolites on distinct leaves, a preferential transport into the upper leaves and a low level of translocation into the lower plant parts was observed in both genetically modified and unmodified tobacco plants (Droege, 1991; Droege-Laser et al., 1994).

Glufosinate has a wide spectrum of activity encompassing monocotyledonous and dicotyledonous species. Due to its limited systemic action, there is no enduring effect on perennial weeds. Examples of weed species that are not, or only weakly, combated by glufosinate are *Viola arvensis, Bromus spp., Lolium spp., Agropyron repens* and *Urtica urens* (Hoechst, 1991). Weeds emerging after herbicide application are not affected.

Glufosinate is rapidly broken down in soil due to microbial degradation. At 20°C, the soil half-life is less than 10 days (Smith, 1988; Dorn et al., 1992). Metabolites arise from oxidative deamination and from acetylation (Dorn et al., 1992). L-glufosinate can be used by microorganisms as a source of

nitrogen (Tebbe and Reber, 1989). There are no special reports on the degradation of the D-enantiomer in soil, however, the fast dissipation of the DL-racemic mixture was found in all soils investigated under laboratory, as well as, field conditions (Dorn et al., 1992; Smith, 1989). The end products of microbial degradation are CO_2 and natural phosphorus compounds. There is also formation of bound residues which are finally mineralized (Dorn et al., 1992).

Section II - Metabolism of Glufosinate-Ammonium in Genetically Modified Plants in Comparison to Non-Transgenic Plants

Because of the widespread use of glufosinate in agricultural practices (non-selective application, as a desiccant, selective application in tolerant crops), the metabolism of glufosinate in sensitive, as well as in glufosinate-tolerant plants, is addressed. If the PAT enzyme is used as part of selectable marker systems of genetically modified plants, lower levels of PAT activity are required compared to glufosinate-tolerant crops for selective field applications of the herbicide.

The metabolism of glufosinate in artificial systems like cell suspension cultures (soybean, wheat, maize) and sterile plants (tobacco, alfalfa, carrot) has been analyzed by Komossa and Sandermann (1992) and by Droege-Laser et al. (1994). After treatment of non-transgenic plants with glufosinate, the unstable intermediate 4-methylphosphinico-2-oxo-butanoic acid (PPO) is formed via deamination. A rapid decarboxylation reaction then results in the stable main metabolite 3-methylphosphinico-propionic acid (MPP) which is non-phytotoxic. Within non-transgenic plants, PPO can also be reduced to form 4-methyl-phosphinico-2-hydroxy-butanoic acid, another final and stable product (Droege-Laser et al., 1994). In contrast to transgenic PAT-expressing plants, there is no direct proof that in non-tolerant plants only the L-isomer is metabolized.

The metabolism of glufosinate in non-tolerant plants is only limited because plants rapidly die after herbicide application. Moreover, if used as a non-selective herbicide in agricultural practice, glufosinate is not intended to be applied directly, except for desiccation purposes. If crop plants have not emerged at the time of application, residues in the crop plants can only be due to uptake from the soil. Studies evaluating the amount and nature of “indirect” uptake have shown that traces, mainly of the major metabolite 3-methylphosphinico-propionic acid (MPP), can be found (Hoerlein, 1994). This non-phytotoxic metabolite is also a well known soil metabolite (Tebbe and Reber, 1988) which can be taken up by the roots. It was found to be the only relevant residue following normal weed control in non-transgenic plants (Hoerlein, 1994). In desiccation, residues consist of unchanged glufosinate, with small portions of MPP and a non-relevant portion of 2-methyl-phosphinico-acetic acid.

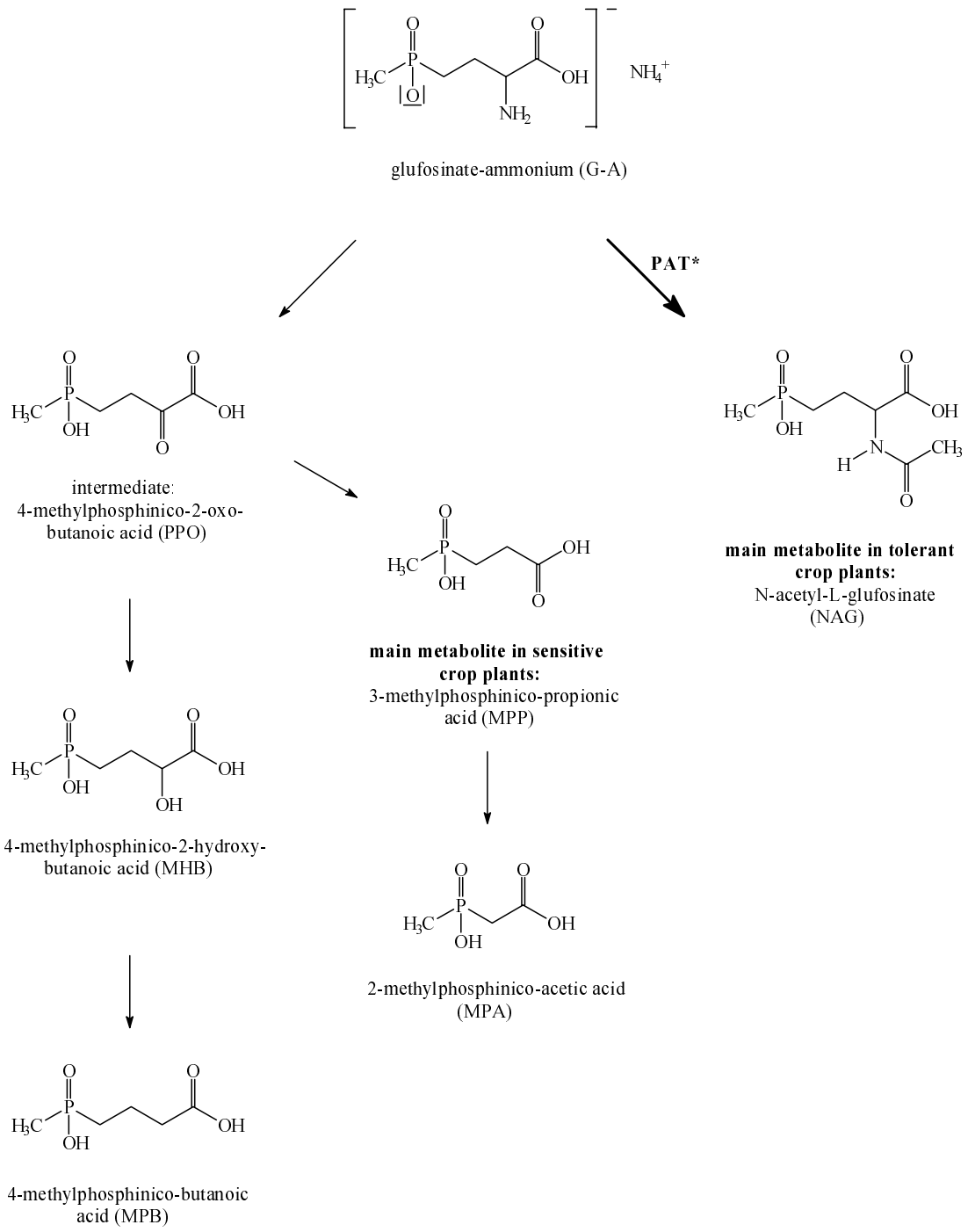
The insertion of genes encoding phosphinothricin acetyltransferase (PAT) enables plants genetically modified in this way to rapidly metabolize the herbicidal active moiety of glufosinate-ammonium into the non-phytotoxic metabolite N-acetyl-L-glufosinate (2-acetamido-4-methylphosphinico-butanoic acid). This metabolite is not found in non-transgenic plants.

The metabolism of glufosinate-ammonium following direct application on genetically modified glufosinate-tolerant corn (maize), oilseed rape (canola), tomato, soybean and sugar beet (Figure 1) has been investigated with the formulated test substance (Burnett, 1994; Tshabalala, 1993; Thalacker, 1994; Stumpf, 1995; Rupprecht and Smith, 1994; Rupprecht et al., 1995; Allan, 1996). In all glufosinate-tolerant crops, the principal residues were N-acetyl-L-glufosinate and - usually with lower concentrations – glufosinate-ammonium and MPP. In corn grain and rape seed, the main residue identified was MPP, with lower concentrations of N-acetyl-L-glufosinate. In corn forage, in soybean seed, in sugar beet roots and in tomato fruit, the main residue was N-acetyl-L-glufosinate. Experiments of Droege et al. (1992) and

Droege-Laser et al. (1994) using transgenic tobacco, carrot, and alfalfa plants also found N-acetyl-L-glufosinate as the major metabolite in glufosinate-tolerant plants. Besides the principal residues, trace levels of other metabolites were also identified in soybean including 2-methylphosphinico-acetic acid (MPA) and 4-methylphosphinico-butanoic acid (MPB). The herbicidally inactive D-glufosinate appears to be stable in plants due to the L-specific acetylation activity of the PAT enzyme. (Droege et al., 1992).

In genetically modified glufosinate-tolerant plants expressing the PAT enzyme, it appears that two metabolic routes compete: (1) the deamination of glufosinate and subsequent conversion of 4-methyl-phosphinico-2-oxo-butanoic acid (PPO) to 3-methylphosphinico-propionic acid (MPP) or to 4-methyl-phosphinico-2-hydroxy-butanoic acid, and (2) the N-acetylation of L-glufosinate by PAT (Droege-Laser et al., 1994). The second of these two routes predominates when PAT specific activity is relatively high.

If genetically modified plants express the PAT enzyme at a low level, the deamination pathway with the formation of MPP predominates. In this case, besides substantial amounts of the acetylated and non-acetylated forms of L-glufosinate, the metabolites 4-methyl-phosphinico-2-oxo-butanoic acid (PPO), 3-methylphosphinico-propionic acid (MPP) and 4-methyl-phosphinico-2-hydroxy-butanoic acid are formed (Droege-Laser et al., 1994).



*) PAT = phosphinothricin acetyl - transferase

Figure 1: Metabolism of Glufosinate-Ammonium in Non-Transgenic and in Transgenic, Tolerant Crop Plants (Corn, Oilseed rape, Tomato, Soybean, Sugar beet) (derived from FAO, 1998)

Section III - Metabolites and Residues in Genetically Modified Plants

The FAO's Joint Meeting of Experts on Pesticide Residues (JMPR) suggested, in 1998, a revised residue definition, considering the nature of the residue occurring in conventional and transgenic glufosinate-tolerant plants. This definition was confirmed by the 1999 JMPR as suitable for the establishment of maximum residue levels and for the estimation of dietary intake. For glufosinate-ammonium, residue is defined as the sum of glufosinate-ammonium, MPP and N-acetyl-L-glufosinate (FAO, 1998).

For residue studies, glufosinate-ammonium and the principal metabolites N-acetyl-glufosinate and 3-methylphosphinico-propionic acid (MPP) are extracted from finely ground sample material with water. After cleaning-up of the extracts, the residues are derivatised, resulting in the formation of methylated/acetylated derivatives. These are cleaned up and determined by gas chromatography using a phosphorus-specific flame photometric detector, yielding analytical recoveries which are satisfactory on many substrates. Glufosinate-ammonium and N-acetyl-L-glufosinate are determined as a common derivative and MPP is quantified as a separate derivative. If a differentiation between glufosinate-ammonium and N-acetyl-L-glufosinate is required, the two compounds need to be separated prior to derivatisation.

Using this procedure, the following individual total residues represented as the sum of glufosinate-ammonium, N-acetyl-L-glufosinate and MPP were obtained from genetically modified, glufosinate-tolerant plants while the limit of quantification for each analyte was 0.05 mg/kg. Individual residue data are mainly part of national submissions for glufosinate-ammonium.

1. **Oilseed rape**

   At an application rate of 750 g/ha or 2 x 800 g/ha, the total residue in the seed at harvest encompasses between < 0.05 and 0.24 mg/kg. Rapeseed oil was found to contain below 0.05 mg/kg total residue.

2. **Corn**

   At an application rate of 400 + 500 g/ha or 2 x 800 g/ha, the total residue in corn grain was between < 0.05 and 0.07 mg/kg. Corn oil contained less than 0.05 mg/kg total residue.

3. **Soybean**

   At an application rate of 400 + 500 g/ha, the total residue in soybean seed ranged from 0.32 to 1.88 mg/kg.

4. **Sugar beet**

   At an application rate of 2 x 600 g/ha or 2 x 800 g/ha, the total residue in roots which are relevant to human nutrition as a raw material for sugar production, were found to be between < 0.05 and 0.88 mg/kg. Refined sugar after processing contained no residues (< 0.05 mg/kg).

The lowest NOEL (no observed effect level), established in a chronic (24 months) feeding study in rats, was 2 mg glufosinate-ammonium/kg body weight/day (Ebert et al., 1990). This low toxicity is due to the mode of action of glufosinate. In mammals, glufosinate-ammonium competitively inhibits glutamine synthetase (GS). However, contrary to the situation in plants, fixation of ammonia is guaranteed by several metabolic pathways in order to maintain homeostasis of the amino acid pool. The biosynthesis of glutamine from glutamate forms only one of the possibilities for fixation of ammonia and amino groups. Thus GS is only of minor importance for ammonia fixation in mammals. In this context, Hack et al. (1994) found that inhibition of glutamine synthetase by glufosinate did not essentially affect the level of ammonia, glutamate and other amino acids. Since the toxicological data indicated no genotoxic, carcinogenic or teratogenic potential, an acceptable daily intake (ADI) value of 0.02 mg/kg body weight/day was accepted for glufosinate (WHO, 1992). This value has been confirmed as group ADI for glufosinate-ammonium, MPP and N-acetyl-L-glufosinate (WHO, 1999).

Tolerances for combined residues of glufosinate-ammonium and its metabolites (3-methylphosphinicopropionic acid and N-acetyl-L-glufosinate) have been established in the USA for transgenic field corn and transgenic soybean. The tolerances are 0.2 mg/kg and 2.0 mg/kg for corn grain and for soybean seed, respectively (EPA, 1999).

Glufosinate-ammonium is registered for the use in the following transgenic tolerant crops:

Canada	Canola and Corn
USA	Corn and Soybean
Germany	Corn
Portugal	Corn
Argentina	Corn
Romania	Corn

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