# A Review of the Food and Feed Safety of the PAT Protein

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## INTRODUCTION

This document provides a comprehensive review of information and data relevant to the food and feed safety assessment of the protein phosphinothricin-N-acetyl transferase (PAT) produced in genetically engineered (GE)[1] plants by genes isolated from *Streptomyces viridochromogenes* (pat gene) or *Streptomyces hygroscopicus* (bar gene) To date, regulatory authorities in 20 different countries or regions including the European Union (EU) have issued approvals for food and feed uses of GE plants expressing the PAT protein, either by itself or in combination with other GE traits (Table 1), representing112 transformation events and includes 7 species of plants: chicory, cotton, maize, rape (oilseed rape and turnip rape), rice, soybean, and sugar beet. In total, there are about 460 regulatory approvals in these countries[2].

All sources of information reviewed herein were publicly available and include: dossiers presented to regulatory authorities; decision summaries prepared by regulatory authorities; peer-reviewed literature; and product summaries prepared by product developers. Many GE plants contain the pat or bar gene for use as a selectable marker during development. In those cases, there are one or more additional transgenes expressed in the plant and the final product is not necessarily glufosinate tolerant. Although this document will not address these additional genes and phenotypes, their presence should be noted when looking at data on the GE plants that express PAT.

The risk assessments in the source documents typically involve comparisons of the transgenic event to an non-GE parent line and/or closely related isoline, and also use baseline knowledge of the relevant plant species [1]–[8]. The objective of these comparisons is to identify potential risks that the GE plant might present beyond what is already accepted for similar plants by identifying meaningful differences between the GE crop and its conventional counterpart. Any identified differences that have the potential to cause relevant adverse effects can subsequently be evaluated for likelihood and consequences.

The Codex Alimentarius Guidance CAC/GL 45-2003 (Codex Guidance) covers safety assessment of foods derived from GE plants [2], and provides a framework for conducting food safety assessment on GE plants. Safety assessments related to the use of GE plants in food and feed are conducted on a case-by-case basis, taking into account the following factors:

- The biology of the unmodified plant;
- The traditional uses of the unmodified plant in food and feed;
- The intended uses of the GE plant in food and feed;
- The nature of the transgene, the donor organism, and the protein it produces;
- The phenotype conferred by the transgene;
- Compositional analyses of key components including metabolites;
- The presence of known toxins, allergens, and anti-nutritional substances;
- Toxicologic and allergenic properties of the expressed protein;
- Feeding studies for GE plant that is intended to confer nutritional improvement;
- The potential impact of food and feed processing on safety.

**Key words**

PAT, *Bacillus thuringiensis*, insect resistance, genetically engineered, environmental risk assessment



[1]GE crops are crops that have been modified using techniques of modern biotechnology to impart one or more desirable traits such as protection from insects, resistance to herbicides, and improved nutrient profiles.

[2]Regulatory approval should not be interpreted as an indication that the product is in commercial production. There are many examples of products that were granted regulatory approval but were never commercialized, or if they were, have been subsequently discontinued.

**Table 1. Global regulatory approvals of PAT events in GE crops for food and/or feed uses [9].**

| Species | Event Name | Argentina | Australia | Brazil | Canada | China | Columbia | El Salvador | EU | Japan | Korea | Malaysia | Mexico | Philippines | Russia | Singapore | South Africa | Switzerland | Taiwan | Uruguay | USA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Gossypium hirsutum*** **(Cotton)** | 3006-210-23 | | | | x | | | | | | | | x | | | | | | | | x |
| | 281-24-236 | | | | x | | | | | | | | x | | | | | | | | x |
| | 281-24-236 x 3006-210-23 (MXB-13) | | x | x | | | | | x | x | x | | x | | | | | | | | x |
| | 281-24-236 x 3006-210-23 x MON88913 | | | | | | | | | x | | | x | | | | | | | | |
| | 281-24-236 x 3006-210-23 x COT102 × MON88913 | | | | | | | | | x | | | | | | | | | | | |
| | 281-24-236 x 3006-210-23 x 1445 | | | | | | | | | x | | | x | | | | | | | | |
| | LL25 | x | x | x | x | x | | | x | x | x | | x | | | | x | | | | x |
| | GHB614 x LL25 | | | x | | | | | x | x | | | | | | | | | | | |
| | LL25 x 15985 | | | | | | | | | x | x | | x | | | | | | | | |
| | GHB614 x LL25 x 15985 | | | | | | | | | x | | | | | | | | | | | |
| | T304-40 | | x | x | x | x | | | x | x | | | | | | | | | | | x |
| | GHB119 | | x | x | x | x | | | | x | x | | | | | | | | | | x |
| | T304-40 x GHB119 | | | x | x | | | | | | x | | | | | | | | | | x |
| | GHB 614 x T304-40 x GHB119 | | | x | | | | | | x | x | | | | | | | | | | |
| | MON88701 | | x | | x | | | | | x | | | | | | | | | | | x |
| | MON88701 x MON88913 | | | | | | | | | x | | | | | | | | | | | |
| | MON88701 x MON15985 x MON88913 | | | | | | | | | x | | | | | | | | | | | |
| | DAS-81910-7 | | x | | x | | | | | x | | | | | | | | | | | x |
| ***Zea mays*** **(Maize)** | 676, 678 and 680 | | | | | | | | | | | | | | | | | | | | x |
| | DLL25 (B16) | | | | x | | | | | x | | | | x | | | | | | | x |
| | T14 | | | | x | | | | | x | | | | | | | | | | | x |
| | T25 | x | x | x | x | x | x | | x | x | x | x | x | x | x | | | | | | x |
| | T25 x MON810 | | | | | | | | | x | | | | | | | | | | | |
| | NK603 × T25 | | | | | | | | x | x | x | | x | | | | | | | | |
| | DBT418 | | x | | x | | | | | x | x | | | x | | | | | x | | x |
| | Bt-176 | x | x | | x | x | | | x | x | x | | | x | | | x | x | x | | x |
| | Bt10 | | | | | | | | | x | | | | | | | | | | | |
| | Bt-11 | | x | | | | | | x | x | | | | x | | | | | | | |
| | Bt11 x GA21 | x | | x | | | | | x | x | x | | x | x | | | x | | | x | |
| | Bt11 x MIR604 | | | | | | | | x | x | x | | x | x | | | x | | | | |
| | Bt11 x MIR604 x GA21 | | | | | | | | x | x | | | x | x | | | x | | | | |
| | Bt11 x MIR162 x GA21 | x | | x | | | | | | x | x | | | x | | | x | | | x | |
| | Bt11 x MIR604 x MIR162 x GA21 | x | | | | | | | | x | x | | | x | | | x | | | | |
| | 1507 | x | x | x | x | x | x | x | x | x | x | x | x | x | | | x | | | x | x |
| | Bt11×MIR162× 1507×GA21 | | | | | | | | | x | | | | x | | | | | | | |
| | Bt11 x MIR162 | | | | | | | | | x | | | | | | | | | | | |
| | 1507 x NK603 | x | | x | | | | | x | x | | | x | x | | | x | | | x | |
| | Bt11 × MIR604 × 1507 × 5307 × GA21 | | | | | | | | | x | | | | | | | | | | | |
| | Bt11 × MIR162 × MIR604 × 1507 × 5307 × GA21 | | | | | | | | | x | | | | | | | | | | | |
| | 3272×Bt11×MIR604×G21 | | | | | | | | | x | x | | x | x | | | | | | | |
| | TC1507 x MON810 | x | | x | | | x | | | | x | | x | x | | | x | | | | |
| | TC1507 x MON810 x NK603 | | | x | | | | | | x | | | | | | | | | | | |

| Species | Event Name | Argentina | Australia | Brazil | Canada | China | Columbia | El Salvador | EU | Japan | Korea | Malaysia | Mexico | Philippines | Russia | Singapore | South Africa | Switzerland | Taiwan | Uruguay | USA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Zea mays*** **(Maize)** | TC1507 x MIR604 x NK603 | | | | | | | | | x | | | | | | | | | | | |
| | TC1507 x MON810 x MIR604 x NK603 | | | | | | | | | | x | | | | | | | | x | | |
| | TC1507 x MON810 x MIR162 | | | x | | | | | | x | x | | | | | | | | x | | |
| | 1507 × MON810 × MIR162 × NK603 | | | | | | | | | x | x | | x | x | | | | | x | | |
| | MON89034 x 1507 x MON88017 x 59122 | | | | | | | | | x | x | | x | x | | | x | | x | | |
| | All subcombinations of MON89034 x 1507 x MON88017 x 59123 | | | | | | | | x | | | | | | | | | | | | |
| | MON89034 X TC1507 X NK603 | | | x | | | | | x | x | | | | x | | | | | | | |
| | All subcombinations of MON89034 X TC1507 x NK603 | | | | | | | | x | | | | | | | | | | | | |
| | MON89034 X TC1507 x NK603 x DAS40278 | | | | | | | | | x | | | | | | | | | | | |
| | MON87427 × MON89034 × 1507 × MON88017 × DAS-59122-7 | | | | | | | | | x | | | | | | | | | | | |
| | DAS-59122-7 | | x | | x | x | x | | x | x | x | | x | x | | x | x | | | | x |
| | 1507x DAS-59122-7 | | | x | | | | | x | x | x | | x | x | | | x | | | | |
| | 1507 × 59122 × MON810 × NK603 | | | | | | | | | x | | | | | | | | | | | |
| | 1507 × 59122 × MON810 × NK603 × MIR604 | | | | | | | | | x | | | | | | | | | | | |
| | Bt11 x 59122 × MIR604 × 1507 × GA21 | | | | | | | | | x | x | | x | x | | | | | x | | |
| | 4114 | | x | | x | | | | | x | x | | x | | | | | | x | | x |
| | 59122 x NK603 | | | | x | | | | x | x | x | | x | x | | | x | | | | |
| | 59122x1507xNK603 | | | | x | | | | x | x | x | | x | x | | | x | | | | |
| | MS3 | | | | x | | | | | | | | | | | | | | | | x |
| | DAS-06275-8 (TC6275) | | | | x | | | | | x | | | | | | | | | | | x |
| | Bt11 (X4334CBR, X4734CBR) | x | x | x | x | x | x | | x | x | x | | x | x | | | x | x | | x | x |
| | 33121 | | | | | | | | | x | | | | | | | | | | | |
| | 186165 | | | | | | | | | x | | | | | | | | | | | |
| | 186169 | | | | | | | | | x | | | | | | | | | | | |
| | 187156 | | | | | | | | | x | | | | | | | | | | | |
| | 43A47 | | | | | | | | | x | | | | | | | | | | | |
| | 40416 | | | | | | | | | x | | | | | | | | | | | |
| | 32316 | | | | | | | | | x | | | | | | | | | | | |
| | CBH-351 | | | | | | | | | | | | | | | | | | | | x |
| | MS6 | | | | | | | | | | | | | | | | | | | | x |
| ***Glycine max*** **(Soybean)** | A2704-12 | x | x | x | x | x | x | | x | x | x | x | x | x | x | | x | | | x | x |
| | A2704-21 | x | | x | x | x | x | | x | x | x | x | x | x | x | | x | | | x | x |
| | A5547-35 | x | x | x | x | x | x | | x | x | x | x | x | x | x | | | | | | |
| | A5547-127 | x | x | x | x | x | x | | x | x | x | x | x | x | x | x | | | | x | x |
| | DAS-68416-4 | | x | x | x | | | | | x | x | | | | | | | | | | x |
| | DAS-68416-4 x MON89788 | | | | | | | | | x | | | | | | | | | | | |
| | DAS-44406-6 | | x | | x | | | | | x | x | | x | | | | x | | x | | x |
| | SYHT0H2 | | x | | x | | | | | x | x | | | | | | | | | | x |
| | DAS-81419-6 | | x | | x | | | | | x | | | | | | | | | | | x |
| | MON87708 | | | | x | | | | | | | | | | | | | | | | |

| Species | Event Name | Argentina | Australia | Brazil | Canada | China | Columbia | El Salvador | EU | Japan | Korea | Malaysia | Mexico | Philippines | Russia | Singapore | South Africa | Switzerland | Taiwan | Uruguay | USA |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Glycine max*** **(Soybean)** | DAS21606 | | | | | | | | | x | | | | | | | | | | | |
| | GU262 | | | | | | | | | | | | | | | | | | | | x |
| | W62, W98 | | | | | | | | | | | | | | | | | | | | x |
| ***Brassica rapa*** **(Canola)** | HCN28 (T45) | | x | | x | x | | | x | x | x | | x | | | | | | | | x |
| | HCR-1 | | | | x | | | | | | | | | | | | | | | | |
| | HCN10 (Topas 19/2) | | | | x | | | | | x | | | | | | | | | | | x |
| | HCN92 (Topas19/2) | | | | x | x | | | | x | x | | x | | | | x | | | | x |
| | MS1 | | x | | x | x | | | | | | | | | | | | | | | |
| | RF1 | | x | | x | | | | | | | | | | | | | | | | |
| | MS1 x RF1 | | x | | x | x | | | x | x | x | | | | | | x | | | | x |
| | RF2 | | x | | x | | | | | | | | | | | | | | | | |
| | MS1 x RF2 | | x | | x | x | | | x | x | x | | | | | | x | | | | x |
| | RF3 | | x | | x | | | | x | x | | | | | | | | | | | x |
| | MS8 | | x | | x | | | | x | x | | | | | | | | | | | x |
| | MS8 x RF3 | | x | | x | x | | | x | x | x | | x | | | | x | | | | x |
| | MS8 x RF3 x RT73 | | | | | | | | | x | | | | | | | | | | | |
| | B91-4, B93-101 and B94-2 | | | | | | | | | | | | | | | | | | | | x |
| | PHY14, PHY35 | | | | | | | | | x | | | | | | | | | | | |
| | PHY36 | | | | | | | | | x | | | | | | | | | | | |
| ***Oryza sativa*** **(Rice)** | LLRICE62 | | x | | x | | | | | | | | x | x | | | x | | | | x |
| | LLRICE06 | | | | x | | | | | | | | x | | | | x | | | | x |
| ***Beta vulgaris*** **(Sugar Beet)** | T120-7 | | | | x | | | | | x | | | | | | | | | | | x |
| ***Cichorium intybus*** **(Chicory)** | RM3-3, RM3-4, or RM3-6 | | | | | | | | | | | | | | | | | | | | x |

Table 1 Notes:

[1] An "X" means an approval. This table presents information on regulatory authorizations that have been granted for food and feed use of the indicted GE plants. It does not consider the timeframe for any authorizations, and should not be used to determine if a particular plant is currently on the market in any particular jurisdiction.

[2] Existing stacked event authorizations are included in this table because they rely on safety data relevant for assessing the safety of the PAT protein. Some countries (such as the United States) do not require regulatory approval for "stacked events" that are generated through conventional breeding of two or more approved GE plants.

Since this monograph is on the safety of the PAT protein and not on GE crops containing the protein, not all the safety assessment elements in the Codex Guidance are relevant. The three topics covered in this monograph are "Origin and Function of PAT" (including its mechanism of action on targeted species), "Expression of PAT in Phosphinothricin-Tolerant GE Plants" (including the expression levels of PAT in various parts of the crops), and "Food and Feed Safety of the PAT Protein" (including information on toxicology and allergenicity assessments).

## ORIGIN AND FUNCTION OF PAT

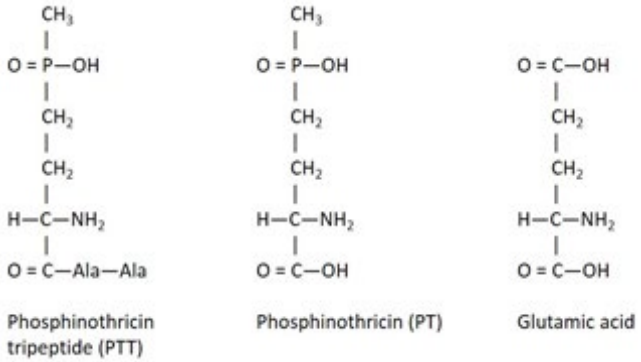
### Phosphinothricin, bialaphos, and glufosinate ammonium

In the early 1970s a previously unknown amino acid was isolated independently from two species of *Streptomyces* by laboratories working in Germany (from *Streptomyces viridochromogenes*) and Japan (from *Streptomyces hygroscopicus*) (*Bayer et al., 1972; Kondo et al., 1973; OECD, 1999*). Originally seen as a tripeptide with two alanine residues (see Fig. 1), the new amino acid (L-2- amino-4-[hydroxyl(methyl)phosphinyl] butyric acid) was given the name phosphinothricin (PT) and the tripeptide called phosphinothricin tripeptide (PTT) or bialaphos (sometimes as "bilanafos" or "bilanaphos") [10]. In Germany, racemic mixtures of PT were

produced (D,L-phosphinothricin and D,L-PPT) and determined to have herbicidal activity. D,L-PPT- ammonium, referred to by the common name glufosinate ammonium (GLA) is the active ingredient in herbicide formulations marketed worldwide. In Japan, the bialaphos tripeptide was observed to have herbicidal activity and this has been commercialized as well [10].

Phosphinothricin inhibits the activity of the glutamine synthetase enzyme (GS) by competitively binding in place of the normal substrate, glutamate (glutamic acid). This prevents the synthesis of L-glutamine, which is not only an important chemical precursor for the synthesis of nucleic acids and proteins, but serves as the mechanism of ammonia (NH3) incorporation for plants [10], [11]. Treatment with phosphinothricin causes accumulation of ammonia and cessation of photosynthesis, probably due to the lack of glutamine [10], [11].

**Figure 1. The structure of phosphinothricin, PTT and glutamic acid (Figureis from Schwartz et al.**, 2004).




### Mechanism of phosphinothricin tolerance

The identification of the plant GS inhibitor phosphinothricin from *Streptomyces* suggested that these Streptomyces bacteria employ a biochemical mechanism to preserve endogenous GS activity for their own survival. In the late 1980s, two genes were identified independently based on their ability to confer resistance to phosphinothricin inhibition of GS, both of which encode a phosphinothricin acetyl transferase protein (PAT). The bialaphos resistance gene, bar, was isolated from *S. hygroscopicus* while the homologous gene from *S. viridochromogenes* was termed pat after the function of the enzyme [12]–[14]. Both genes have been used extensively in genetic engineering of crop plants. They both code for proteins that consist of 183 amino acids, with a sequence identity of 85% [12], [14], [15]. Importantly, both proteins acetylate phosphinothricin but show no activity with glutamate, which is structurally similar, or with any other amino acids tested, indicating a high specificity [12], [13], [15]. The only recorded differences in activity between the two proteins are minor differences in the optimal pH, and a significantly different affinity for acetyl-coA (a co-substrate); these differences are not expected to be meaningful *in planta* [12], [15]. Because the PAT proteins encoded by *bar* and *pat* are structurally and functionally equivalent, with similar molecular weights, immuno-cross-reactivity, substrate affinity and specificity, they are considered together in this document and will both be referred to as the PAT protein.

The PAT enzyme acetylates phosphinothricin at the N-terminus. N-acetyl phosphinothricin has no herbicidal activity, and resistance is therefore conferred through modification of the herbicide rather than the target of its activity [12]–[15].

## EXPRESSION OF PAT IN PHOSPHINOTHRICIN-TOLERANT GE PLANTS

It is important to know the concentration levels of PAT protein in various parts of the GE plants because these levels, together with consumption information, can be used to estimate the human exposure for food safety assessment and animal exposure for feed safety assessment. The *pat* or *bar* gene introduced in some transformation events (such as soybean lines DAS-68416-4 and DAS-44406-6) was directly derived from bacteria with no change in DNA sequence [16]–[41]. In some other transformation events (such as soybean lines A2704-12 or A5547-127), the PAT protein is encoded by a synthetic *pat* gene, which shares about 70% structural similarity with the native *pat* gene from *S. viridochromogenes* [42]–[47]. There are also some other cases where minor changes were made at gene level [48]–[57]. Regardless, the amino acid sequence of the synthetic PAT protein is 100% identical to that of the native protein [16]–[18], [42]–[53], [58], [59]. However, in some events where *bar* gene is modified, the PAT protein also has a slight change in amino acid sequence [60]–[69].

Data for the level of expression of PAT in phosphinothricin-tolerant GE plants that have obtained regulatory approvals are available in publicly accessible regulatory documents [16]–[21], [23]–[53], [55]–[59], [61], [63]–[166]. In obtaining these expression data, issue types tested and sampling methodologies vary greatly. The most common method uses enzyme-linked immunosorbent assay (ELISA) to quantify the amount of protein present in a given sample, but other methods include an assay for enzymatic activity and the use of Northern blots to quantify mRNA. Normally, one or more samples are collected from plants in field trials or greenhouse experiments and the amount of protein is given as a mean value accompanied by either a standard deviation or a range of observed values to show variability. The result is often quantified as a ratio to the dry weight of the sample (*e.g.* µg PAT/g dry weight), but some reports calculate the ratio to the fresh weight of the sample or to the total extractable protein from the sample (*e.g.* µg PAT/g total protein).

Variations in methodology for both sample collection and subsequent analysis make direct statistical comparisons of the data inappropriate. However, the weight of evidence suggests the PAT protein is expressed at low levels relative to typical nutrient proteins or is undetectable in the GE plants [16]–[21], [23]–[53], [55]–[59], [61], [63]–[166]. Therefore, exposure to the protein through consumption of food derived from these crops would be minimal. The *pat* gene was used as

a selectable marker in some events and the PAT protein may or may not be present in the commercial-stage GE plants [49]. The highest reported levels of expression observed in each species using ELISA are reported in Table 2.

**Table 2. Highest reported expression level of the PAT protein in GE plant tissues from representative approved events[1].**

| Species | Event | Expression Level (ng/g fresh weight) | Tissue | Reference |
|---|---|---|---|---|
| *Beta vulgaris* (Common beet) | T120-7 | 966[4] | Top[2] | [146] |
| *Brassica napus* (Rapeseed) | Topas19/2 | 944[4] | Leaf | [152] |
| *Glycine max* (Soybean) | SYHT0H2 | 53090±50910[3,7] | Leaf | [48] |
| *Gossypium hirsutum* (Cotton) | T304-40 | 222000[4] | Seed | [83] |
| *Oryza sativa* (Rice) | LLRICE62 | 84700[4] | Leaf | [155] |
| *Zea mays* (Maize) | DAS-06275-8 | 935000[4,5] | Leaf | [167] |
| *Cichorium intybus* (Chicory) | RM3-3 | 0.63%[6] | Leaf | [150] |

Table 2 Notes:
[1] These values are not cross-comparable due to differences in sample collection and preparation methodology.
[2] Top refers to all above-ground tissue (i.e. leaves and stems).
[3] Reported as mean ± standard deviation.
[4] Reported as ng/g fresh weight.
[5] Represents the highest value in a reported range.
[6] Expressed as per total protein.
[7] Reported as ng/g dry weight.

Despite that some small differences were found in the levels of a few measurement endpoints in compositional analysis of whole crops, these differences were determined to be biologically insignificant, which further support the lack of unintended effects as a result of the genetic modifications [16]–[18], [42]–[53], [56]–[59], [71]–[94], [142]–[212]. It is also considered unlikely that the PAT protein could affect the metabolic system of the recipient plant [60], [61], [63]–[69], [95]–[141], [207], [213]–[233].

## FOOD AND FEED SAFETY OF THE PAT PROTEIN

### General considerations in assessing food and feed safety of GE crops

In assessing food safety for GE crops, comparative assessment is a key step, though it is not a safety assessment by itself. This concept is used to identify similarities and differences between the new food and its conventional counterpart. It helps to identify potential safety and nutritional issues and therefore this method overall is widely accepted as a useful method to assist safety evaluation of GE crops [2]. When statistical differences are identified between a GE crop and its conventional counterpart for the levels of some substances, the biological relevance needs to be assessed for these differences. A difference is considered to have no biological relevance when the level of the substance in the GE crop is within the natural variation observed in the population of conventional crop varieties with confirmed history of safe use. However, the criteria for evaluating biological relevance are often subject to dispute, despite the overall wide acceptance of comparative assessment as an approach to GE safety evaluation. A recent study set up a model for deriving reasonable natural variations in the form of tolerance intervals which holds hope for eliminating dispute on the issue of determining biological relevance for a statistically significant difference [234]. It was found in another study that the identified differences between the GE and its comparator varieties are not attributed unequivocally to the GM trait, but due to minor genomic differences in these comparator varieties [235].

Regulatory agencies around the world regulate GE crops for food and/or feed use based on safety assessment of the specific GE crop products. Although countries follow the same Codex guidance, the data requirements for regulatory approvals are not the same in all countries/regions.

According to Codex Guidance CAC/GL 45-2003 [2], when assessing potential toxicity of an expressed protein in GE crops, the following aspects should be considered: primary sequence similarity between the protein and known protein toxins and anti-nutrients, stability to heat or processing and to enzymatic degradation, and oral toxicity studies in cases where the protein present in the food is not similar to proteins that have previously been consumed safely in food. In addition, allergenicity of the protein should be assessed with additional consideration of the possibility of causing gluten-sensitive enteropathy, if the introduced genetic material is obtained from wheat, rye, barley, oats, or related cereal grains [2]. When the transformed crop has known allergenic properties (e.g. soybean, peanut, rice, etc.), then the level of endogenous allergenic proteins should not be increased in the GE crop.

In the United States, the Food and Drug Administration (FDA) is in charge of food safety of whole GE plants that contain PAT. FDA assesses food safety of GE proteins introduced into the plants by focusing on toxicity and allergenicity. Before the proteins are introduced into the food or feed supply, they are tested for heat and digestive stability, as well as their structural similarity to known allergenic proteins [237].

In Canada, Health Canada regulates foods, and the Canadian Food Inspection Agency (CFIA) regulates livestock feed [238]. Health Canada regulates GE food through its authority over novel foods. Toxicology studies are not considered necessary if the substance of

interest or a closely related substance has a safe consumption history at equivalent consumption levels or if the new substance is not present in the food. Otherwise, conventional toxicology studies on the new substance are required. The toxicity assessment of proteins covers structural homology, stability to heat, processing, and enzymatic degradation. If the expected exposure is oral only, it is generally not necessary to study long-term toxicological effects (direct-acting carcinogens, mutagens, teratogens or reproductive toxicants). Acute oral toxicity studies on the novel proteins are appropriate for assessing their potential toxicity. The detection of unintended changes relies on agronomic and compositional analysis. Besides testing proteins, testing of the whole GE food is also considered, since unexpected changes to the genome, caused as a result of the genetic engineering process, could result in accumulation of toxic substances either of endogenous or exogenous origin [239]. When assessing feed derived from GE crops, CFIA considers nutritional data, toxicological data, allergenicity data, feeding trials, and environmental safety. Feed safety considerations include toxicity to livestock through feed intake and human health through ingestion of livestock food products or occupational exposure or exposure among bystanders [240].

In the EU, European Food Safety Authority (EFSA) is the authoritative agency performing safety assessment for food/feed of GE crops, though it does not have regulatory power. EU requires the newly expressed proteins to be tested in a repeated-dose 28-day oral toxicity study in rodents that should be performed according to OECD guideline 407. Depending on specific profiles, the whole food and feed derived from the GE crop should be tested, and the testing program should include a 90-day toxicity study in rodents. Post market monitoring (PMM) might also be required on a case-by-case basis [241]. However, it is well known that it can be extremely difficult for whole food exposure studies to detect potential adverse effects and attribute these effects conclusively to an individual characteristic of the food [2].

## TOXICOLOGICAL STUDIES ON THE PAT PROTEIN AND GE CROPS

### Toxicity prediction based on genetic stability and bioinformatics

Though not a part of safety assessment, in GE crops with food safety approval, the pat or bar gene has been stably integrated into the plant genome and is stably inherited from one generation to the next [16]–[18], [20]–[38], [40], [42]–[59], [70]–[94], [143], [146], [148]–[153], [155]–[158], [160], [162], [163], [165], [166], [168]–[182], [187]–[206], [208], [212], [242]–[244]. In addition, comparative structural analyses with known toxins do not indicate any potential for the protein to be toxic to humans [16]–[55], [58], [63], [67], [69], [70], [92], [94], [112], [123], [125], [126], [129], [136], [143], [146], [148]–[153], [155]–[158], [160], [162], [163], [165], [166], [168]–[172], [187], [188], [191]–[208], [212], [228], [232], [233], [243]–[248]. The databases searched were generally latest versions of protein toxin databases at the time of search, such as Swissprot, GenBank, Entrez, EMBL, and PIR. BLASTP search program was often used when comparing the structure of interest with structures in the databases [150][158][162][163][142][143][145].

The PAT protein is also inactivated by heating [20], [21], [23]–[35], [37]–[39], [41]–[49], [54]–[56], [58], [71]–[76], [78]–[94], [142], [143], [146], [150], [162], [168]–[179], [181], [182], [244]. The PAT protein is also rapidly digested in simulated gastric (SGF) and intestinal fluids (SIF) [249]. For example, PAT from a crude protein extract from glufosinate ammonium tolerant maize leaves was treated with SGF and was found to be digested in less than 5 seconds. Purified PAT in simulated intestinal fluid (SIF) was completely digested within 15 minutes [18], [20], [21], [23]–[48], [52]–[58], [70]–[94], [142], [143], [145], [146], [148]–[152], [155]–[158], [160], [162], [163], [165], [166], [168]–[179], [181], [182], [187]–[208], [212], [227]–[229], [243]–[246], [248].

### Acute toxicity studies of the PAT protein and GE Crops

In many countries where GE crops have been approved as food or feed, acute animal studies are required for assessing toxicity of a newly expressed protein because proteins typically exert toxicity via acute mechanism. In fact, oral exposure to proteins has not been shown to have carcinogenic, teratogenic, or mutagenic effects [250]. In the acute toxicity studies, rodents are exposed orally to the protein at levels up to 5000 mg/kg for up to 14 days. According to numerous regulatory decision documents of various countries, the PAT protein was consistently found to be non-toxic in acute mouse gavage test using purified PAT protein at very high doses [18], [30], [33]–[38], [40], [42]–[48], [50], [57], [58], [71]–[74], [76]–[81], [85]–[93], [145], [149], [157], [158], [162], [165], [168]–[179], [181], [182], [187]–[206], [211], [244], [248]. In the studies assessed in these approval documents, the protein used for testing was often from *Escherichia coli*. Data have demonstrated that the plant-expressed PAT protein and those from alternative sources have the same apparent molecular weight, indicating that the plant-expressed PAT protein does not appear to have undergone any significant post-translational modifications of a type that would alter the molecular weight/electrophoretic mobility of the protein [43] and the two sources of proteins are equivalent [16], [42], [44]–[49], [57], [71], [74]–[81], [83], [86]–[93], [149], [158], [162]. Acute, intravenous toxicity experiments in mice show the PAT protein has no toxicity even at a dose much higher than those that would realistically enter the blood stream following food consumption [249].

### Safety assessment of stacked events

In some countries, GE plants with stacked events (i.e., those with more than one gene introduced typically by cross-breeding two or more GE plant varieties of the same species), where *pat* or *bar* was one of the events, were also assessed for biosafety. Besides the safety data on their parent GE plants, data on possible changes and potential adverse effects (such as gene silencing, metabolic

changes, compositional changes, agronomical changes, toxicity, and allergenicity) as a result of interactions between the introduced genetic modifications are often taken into account when assessing food and feed safety of stacked events. These include possible impact on genetic stability of the introduced traits and level of expression of the involved novel proteins. The authorities came to the conclusion that stacked events, with one event expressing the PAT protein, did not add extra food or feed risk via interactions between the expressed gene products. It is very unlikely that stacked events expressing novel proteins that participate in different metabolic pathways will interact [60], [63]–[65], [67]–[69], [71], [74]–[76], [78]–[81], [84]–[91], [95]–[104], [107], [113]–[120], [122], [124], [126]–[128], [131], [134], [135], [140], [168]–[171], [173]–[179], [215]–[217], [220]–[227], [230]–[233], [247], [248], [251], [252].

### Allergenicity of the PAT protein

One concern with the safety of GE crops is the risk of introducing new allergens or increasing the level of existing endogenous allergens through the introduction of new genes and gene products into the crops. Here the primary focus is on the allergenicity of the PAT protein, not that of the whole GE crops.

Immunoglobulin E (IgE) mediated food allergy (type I food allergy) has two phases: sensitization and elicitation. Sensitization usually occurs by a primary exposure to the given dietary protein in susceptible individuals. In elicitation phase, re-exposure to the same protein leads to a series of biochemical and cellular changes that finally result in allergic symptoms. Since many food allergens are thought to sensitize through the gastrointestinal (GI) tract, resistance to proteolysis in the GI tract has been proposed to be a prerequisite for sensitization [253].

The following aspects are commonly considered when assessing allergenicity hazard of a protein: structural similarity to known allergens, glycosylation status [254], heat stability, the impact of food or feed processing, and enzymatic degradation in SGF [255] and simulated intestinal fluid [6] and in some cases, immunological properties (via IgE binding assays) [253]. Note that IgE binding studies may only be appropriate when the gene donor is a known source of allergens or if structural similarity is found between the protein and known allergens. Since risk depends on exposure, the level of expression in the food for consumption should also be estimated [256]. Although proposed by some scientists [253], studies on the eliciting or sensitizing capacity of proteins are not conducted often since the predictive value or practicality of these assays, especially animal models for sensitization, have not been proven [256]. In fact, there is no validated animal model that is satisfactorily predictive of protein allergenicity, mainly due to a lack of understanding of the detailed mechanism of food-induced allergy [257], [258].The assessment of allergenicity for a protein usually follows a weight-of-evidence approach by taking into account all of the information obtained, since none of the commonly used experimental methods alone can provide confirmatory evidence on allergenicity [4], [241], [255], [259]. Though allergens are typically water-soluble glycoproteins and are stable to treatment with heat, acid or proteases, many food allergens do not share such characteristics and some non-allergenic proteins can have these characteristics. Considering that digestibility assays are not as reliable as previously hypothesized [260], it was proposed that these digestibility assays should be combined with immunological assays to minimize uncertainty in allergenicity assessment [253], [255]. Digestion conditions are known to influence the outcome of the digestibility assay, such that a standard set of conditions should be utilized[261]. In addition, besides the intact proteins, peptide fragments generated during the digestion process, especially those larger than 3.5 kDa, should be assessed for stability and allergenicity [253].

The PAT protein has been determined to not share properties with known allergens. The *pat* gene originates from *Streptomyces viridochromogenes*, bacteria that are generally soil-borne and not typically pathogenic to animals including humans [17], [50]. Amino acid sequence analysis of PAT did not identify any significant similarities to known allergens using the latest AllergenOnline.org database [262] and the PAT protein molecules do not have N-glycosylation sites [142]–[144], [146], [148]–[153], [155]–[158], [160], [162], [163], [165], [166], [208], [212], [249]. The resistance to degradation of the proteins was measured in a pepsin solution at a pH of 1.2 or 2. The integrity of the protein was analyzed by gel electrophoresis followed by protein staining. The stability of PAT in SGF and SIF was also studied and found that they were rapidly digested [18], [20], [21], [23]–[48], [54], [55], [92], [93], [168]–[179], [181], [182], [249]. To address the concern that using a purified protein in digestion assays might not represent the exposure scenario where the exposure is actually a mixture of proteins and other substances, PAT in soluble proteins as well as from leaf tissue powder was examined in SGF and found that PAT degradation in these scenarios was delayed but the degradation was complete after 5 min of digestion, indicating that the PAT protein can still be defined as a protein readily digestible without causing an increased risk of food allergy [263].

Various regulatory approval documents had the same conclusion that the PAT protein does not have characteristics that are typical of known food allergens, and there is no history that the proteins are allergenic [16], [17], [20], [23]–[35], [37]–[39], [41]–[49], [52], [53], [55], [56], [61], [63]–[70], [72], [83], [92]–[144], [146], [148]–[153], [155]–[158], [160], [162], [163], [165], [166], [207], [208], [212], [227]–[230], [232], [233], [243]–[248].

## FEEDING STUDIES ON FOOD AND FEED DERIVED FROM GE CROPS EXPRESSING THE PAT PROTEIN

Feeding studies are generally not designed specifically as toxicity tests but as nutrition studies to evaluate unknown factors that may present in GE crops which affect animal growth and well–being. Such feeding studies are typically of short duration because of the difficulties with

interpreting the results of long–term whole food animal feeding studies [264].

By assessing feeding studies on farmed animals such as rats, chicken, fish, and dairy cattle, regulatory authorities in various countries/regions came to the conclusion that processed or unprocessed meals derived from GE crops do not cause significant health effects in the animals studied [18], [19], [33]–[38], [42]–[48], [50], [57], [71]–[83], [85]–[94], [165], [208], [211].

Besides feeding studies included in regulatory submissions, there are also feeding studies published in the peer-reviewed literature. In a study where three generations of mice were fed genetically engineered rice for 180 days, no allergenicity and mutagenicity endpoints showed positive results [265]. In a study in which rats were exposed to 34% transgenic maize grains expressing PAT for at least 92 days, no biologically significant differences were observed in nutritional performance, clinical including neurobehavioral signs, ophthalmology, clinical pathology, organ weights, and gross and microscopic pathology between rats in treatment and control groups [266]. Similarly, two 90-day feeding studies in rats fed PAT-expressing transgenic Maize lines 1507 and 59122 failed to identify any toxicologically significant differences in the set of endpoints as mentioned above between any pair of treatment groups [267], [268]. A Chinese 90-day feeding study in rats exposed to DAS-59122-7 (59122) transgenic maize did not identify any biologically significant effects [269]. A 12-week feeding study in hens indicates that performance of hens fed diets containing 59122 maize grain, as measured by egg production and egg quality, was similar to that of hens fed diets formulated with near-isogenic maize grain [270]. A 6-week broiler study was conducted with diets containing toasted DAS-68416-4 soybean meal to evaluate nutritional wholesomeness and safety compared with conventional comparators. Broiler growth and performance parameters indicate that DAS-68416-4 soybean is nutritionally equivalent to non-transgenic soybean [271]. A review article summarized findings on feeding studies on food/feed safety of maize event TC1507 and concluded, among others, that TC1507 maize grain did not cause significant toxicological effects in rodents [272].

## CONCLUSION

The PAT protein expressed in GE plants is encoded by one of the homologous genes *pat* or *bar*, isolated from the related bacteria *Streptomyces viridochromogenes* or *Streptomyces hygroscopicus*, respectively. Genetic analyses showed that the introduction of PAT into crops did not impact the genetic stability of the receiving crops. Compositional analyses consistently showed that it does not induce any unintended effects with biological significance. Bioinformatic analyses, *in vitro* studies of the stability of PAT under heating or with presence of gastrointestinal fluids did not identify any property in the protein that is typical of a protein toxin or protein allergen. Various acute oral toxicological studies and feeding studies with either toxicological or nutritional considerations did not find any changes of biological significance. Regulatory agencies across the world evaluated the data in regulatory submissions for more than 100 transformation events containing PAT and they consistently concluded that the presence of this protein in the GE crops does not pose any significant risk in addition to what has already been accepted for conventional crops.

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