Key Messages from the White Paper

"Evaluating the Safety of GM Crops: Lack of Value of Long Term Toxicology Testing"

KEY MESSAGES

- The safety of food can never be proven absolutely. Even substances required for life (*i.e.,* water, sodium chloride, Vitamin C), can be harmful if consumed in excessive quantities.

- There is no scientific basis for conduct of long-term studies of GM traits or crops if no biologically relevant differences have been identified through the comparative assessment process.

- It is unethical to subject animals to toxicity testing for no real benefit for the risk assessment process.

DETAILED REASONING

- The safety of food can never be proven absolutely. Even substances required for life (*i.e.,* water, sodium chloride, Vitamin C), can be harmful if consumed in excessive quantities.

- Traditional foods, even those that naturally contain toxins or anti-nutrients, are not generally subject to any testing because of their overall long history of safe use (HOSU).

- New chemical constituents added to food for functional purposes (*e.g.,* antioxidants, food colorings, preservatives) or as a result of efforts to control pests must undergo toxicity testing in animals when there is insufficient safety information on these substances.

- Food safety testing has traditionally been conducted as a comparative procedure where the new food is compared with its traditional counterpart in order to highlight any meaningful differences. These differences then become the focus of the safety assessment.

- A similar comparative safety assessment is followed for genetically modified (GM) crops and derived foods and feeds. In this approach, the GM crop is compared with its traditional counterpart to determine any biologically meaningful differences.

- The comparative procedure for GM crops focuses on molecular, compositional, phenotypic, and agronomic analyses. In addition, a thorough assessment of the safety is undertaken. The combination of these two testing paradigms (comparative assessment and safety of a new, GM protein) provides a very high level of safety assurance.

- The safety of a newly expressed protein includes:
    1. biochemical function
    2. lack of similarity to known allergens and mammalian protein toxins
    3. similarity to proteins with a history of safe consumption
    4. *in vitro* digestibility
    5. *in vitro* thermodynamic stability
    6. *in vivo* toxicity testing (on a case-by-case basis)

- Acute[1] toxicity evaluations using laboratory animals are usually conducted after a weight of evidence for the newly expressed protein safety already exists (above points). An acute study is appropriate because protein toxins tend to act rapidly.

- A 28-day ("sub-acute"[2]) repeat dose oral toxicity study may be conducted on a case-by-case basis when there is insufficient history of safe use HOSU for the protein.

- Both acute and sub-acute studies provide a high degree of assurance of safety because the newly expressed protein is administered in high doses. An absence of adverse findings in such studies suggests that longer term testing is not warranted.

- Some countries may require a 90-day ("sub-chronic"[3]) feeding study in rodents with high levels of the whole food (*i.e.,* grain) in the diet if the molecular, compositional, phenotypic, or agronomic analyses indicated biologically meaningful differences between the GM and non-GM crop.

    - When there are no differences in the molecular, compositional, phenotypic, and agronomic evaluations, the 90-day study is considered to be "… of little additional value if any…" and, "…therefore not deemed necessary on a routine basis" (EFSA, 2011).

    - If required to be conducted for risk management purposes, the 90-day study is considered to be "…of sufficient duration for the identification of general toxicological effects of compounds that would also give adverse effects after chronic exposure" (EFSA, 2008).

    - In addition to demonstrating that the trait is safe in the whole food, the 90-day study also demonstrates that unintended adverse effects were not created by adding the novel gene to the plant's genome.

- There is evidence that an absence of adverse findings with GM traits and crops in shorter-term tests (acute and sub-chronic studies) is consistent with an absence of adverse findings when administered in a chronic[4] study (*i.e.* longer term, 2 year studies).

    - For example, rats were fed either GM or non-GM soybeans for six months, one year, or two years (Sakamoto et al., 2007; Sakamoto et al., 2008) and the results were consistent with shorter-term tests demonstrating that GM soybeans were safe (Harrison *et al.,* 1996; Hammond *et al.,* 1996).

- There is no scientific basis for conduct of long-term studies of GM traits or crops if no biologically relevant differences have been identified through the comparative assessment process.

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[1] Acute toxicity is defined as the adverse effects occurring within a short time of oral administration of a single dose of a substance or multiple doses given within 24 hours. The cumulative dose whether single or multiple, is usually very high (for reference, see OECD TG 425).

[2] A study performed to obtain information on the toxicity of a substance after repeated administration, typically 14-28 days in duration (for reference, see OECD TG 407).

[3] A repeat dose toxicity study longer than a sub-acute toxicity study, but not to the length of a chronic toxicity study. Sub-chronic studies are typically 90 days in duration (for reference, see OECD TG 408).

[4] Long-term toxicity studies similar to sub-chronic studies except that the period of exposure is longer than 90 days. Chronic toxicity studies in rodents are usually 6-24 months in duration. The ability of a substance to induce cancer is typically evaluated by a specially design chronic toxicity study (for reference, see OECD TG 451).

- Empirical evidence indicates digestible protein does not accumulate systemically (*i.e.,* energy from food may be stored as adipose tissue, but the food itself is not stored intact in the body). Hence, acute and 28-day studies are more than sufficient to confirm the safety of long-term consumption of a protein and chronic testing would be of no additional scientific value.

- Nucleic acids (DNA/RNA) and proteins are necessary and ubiquitous dietary components that are degraded into nucleotides and amino acids, respectively during digestion. The nucleic acids and the proteins introduced in a transgenic plant and consumed through diets are comprised of (and thus degraded into) the same building blocks as conventional foods. Thus, there is no scientific basis to suspect that the consumption of digestible DNA/RNA and proteins will contribute to the initiation (*e.g.,* DNA modification or mutation), promotion (e.g. increase in cell proliferation of decrease in cell death), and/or progression (*e.g.,* chromosome disarrangement) of cancer."

o Due to ethical concerns, many scientific and governmental organizations have developed approaches and regulations to replacing, refining, and reducing the number of animals used in toxicity testing. This is a noble goal and underlies the scientific community's obligation to minimize unnecessary animal testing. Accordingly, applicants conducting animal studies to characterize the safety of substances under regulatory review design each study to answer specific questions with the obligation to prove and justify the real benefit of such animal studies. As aforementioned, with no apparent additional benefit of extending the duration of the safety studies, it is difficult to scientifically and ethically justify the use of hundreds more animals to conduct longer term testing on each product.

REFERENCES

EFSA. 2011. Guidance for risk assessment of food and feed from genetically modified plants. EFSA Journal 2011; 9(5):2150.

EFSA, 2008. Safety and nutritional assessment of GE plants and derived food and feed: The role or animal feeding trials. Report of the EFSA GMO Panel Working Group on Animal Feeding Trials. Food Chem. Tox. 46, S2-S70.

Hammond, B.G., J.L. Vicini, G.F. Hartnell, M.W. Naylor, C.D. Knight, E.H. Robinson, R.L. Fuchs, and S.R. Padgette. 1996. The feeding value of soybeans fed to rats, chicken, catfish and dairy cattle is not altered by genetic incorporation of glyphosate tolerance. Journal of Nutrition 126:717-727.

Harrison, L.A., M.R. Bailey, M.W. Naylor, J.E. Ream, B.G. Hammond, D.L. Nida, B.L. Burnette, T.E. Nickson, T.A. Mitsky, M.L. Taylor, R.L. Fuchs, and S.R. Padgette. 1996. The expressed protein in glyphosate-tolerant soybean, 5-enolpyruvylshikimate-3-phosphate synthase from Agrobacterium sp. strain CP4, is rapidly digested in vitro and is not toxic to acutely gavaged mice. Journal of Nutrition 126:728-740

Sakamoto, Y., Y. Tada, N. Fukumori, K. Tayama, H. Ando, H. Takahashi, Y. Kubo, A. Nagasawa, N. Yano, K. Yuzawa, A. Ogata, and H. Kamimura. 2007. [A 52-week feeding study of genetically modified soybeans in F344 rats]. Shokuhin Eiseigaku Zasshi 48:41-50.

Sakamoto, Y., Y. Tada, N. Fukumori, K. Tayama, H. Ando, H. Takahashi, Y. Kubo, A. Nagasawa, N. Yano, K. Yuzawa, and A. Ogata. 2008. [A 104-week feeding study of genetically modified soybeans in F344 rats]. Shokuhin Eiseigaku Zasshi 49:272-282.