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To whom it may concern:

The risks of foods that have been genetically engineered to produce high concentrations of Lysine

This paper sets out the Sustainability Council of New Zealand's position concerning a proposal to allow amounts of a variety of corn that has been genetically engineered to express elevated [supra-physiological] amounts of the amino acid lysine (LY038), to enter the human food chain in New Zealand.

1. Background

Lysine is one of twenty primary amino acids, which together comprise the bulk of proteins in the body and in foods. These amino acids are encoded by the genetic code. [There are also a larger number of the less frequent, so-called secondary amino acids, which are formed physiologically by chemical modifications of the primary amino acids, but these make up only a minor percentage of most food proteins].

Lysine is one of the nine amino acids that are generally considered to be essential for nutrition in humans and other mammals. [The other eight are isoleucine, leucine, threonine, tryptophan, methionine, histidine, valine and phenylalanine]. The meaning of essential is that they are absolutely required in the diet for health. Dietary lysine deficiency is harmful for humans and other mammals, so ensuring adequate dietary lysine intake is important. Lack of lysine is virtually never a problem with the diet in New Zealand, but relative lack can limit optimal growth performance of some domestic animals used by humans as food.

All amino acids share certain common structural features. However, each amino acid contains a side-chain, which gives each one its unique physical and chemical properties.

Lysine is one of the amino acids that is most reactive – that is, it has a tendency to combine with other chemical substances in the cell or in food, to yield chemical modifications.

2. Lysine reacts in tissues to form toxic AGE products

In particular, lysine in proteins reacts with sugars to form glycoconjugates, which are then amenable to further modification by oxidation, to yield so-called glycoxidation

products, or Advanced Glycation Endproducts (AGEs). These are familiar to us in that they are the agents that cause the “browning” of foods during the processes that lead to spoilage.

It is perhaps less well known that these lysine-containing AGE products have been implicated in the mechanisms that lead to a series of major and important human diseases (or their complications), including atherosclerosis and coronary artery disease, hypertensive heart disease, the cardiovascular complications of diabetes mellitus, and chronic kidney failure, amongst others.

There is strong and increasing evidence that such AGE products, when present in the tissues, lead to or cause many of the manifestations of these serious diseases.

There is also growing evidence that such products are harmful when present in food, and food can be a significant source of AGEs.

It is probable that foods engineered to express high concentrations of lysine will contain increased amounts of such AGE products, since, *inter alia*, the physiological mechanisms that tend to decrease such compounds are liable to be overwhelmed by the high lysine content.

There are thus good reasons to look very carefully at foods engineered to express high lysine content, from a chronic food safety perspective.

3. Unnaturally high levels of reactive substances in cells can induce activity of biochemical pathways that can lead to the formation of toxic substances in tissues

There is a second related but separate *a priori* consideration in this matter.

It is a well known principle in metabolism and pharmacology that the presence of elevated concentrations of a reactive substance can induce the activity of minor pathways, which can in turn lead to the formation of substances not usually present in tissues, or present only in minute amounts.

This principle is possibly best known in the field of medicine that deals with the metabolic basis of inherited disease and also in the area of pharmacotoxicology, where particular drugs often interfere with the metabolism of others by opening up such pathways.

It is likely that this was the process that was responsible for the generation of highly toxic byproducts [including 1,1-ethylidenebis (L-tryptophan) (EBT), in which two molecules of tryptophan are joined together], when the Showa Denko company genetically engineered an organism to produce high amounts of another reactive essential amino acid, tryptophan.

This toxic amino acid byproduct led to the development of a potentially lethal disease in humans, eosinophilic myalgia syndrome, which was likely responsible for severe injury of some thousands of people, mainly in the United States, and the deaths of a smaller number.

4. Need for proper safety assessments

Given the evident uncertainty of the full spectrum of products in such cases, it would be scientifically prudent to apply the same processes as are typically employed for the determination of safety of pharmacological agents, through processes such as those supervised by the US FDA¹ or the EMEA. By these, safety is initially demonstrated in properly-constructed trials undertaken in two species of mammals, of which one must be non-rodent.

Safety testing in living mammals (*in vivo*) is usually supplemented by a series of *in vitro* pharmacological assays where potential interactions are specifically sought and measured.

However, significant adverse effects may not be detected in trials in non-human mammalian species.

Therefore, in the case of experimental pharmacology, a second phase of safety testing in humans is performed.

5. Recommendations

In the case of a food engineered to express supra-physiological concentrations of lysine, a known reactive substance, it would be prudent and responsible to ensure that appropriate tests of safety are performed on all such engineered products.

Conversely, the failure to ensure that such studies have been performed to the required standards, would be hard to defend.

This need is emphasised by the known role of lysine-containing compounds in the mechanism of some of the most serious diseases afflicting mankind, and the growing evidence for their toxicity when consumed in foods.

The currently-available safety data for the proposed high-lysine corn is judged to fall far short of the quality required for adequate pharmacological safety assessment.

Given that the application is for this substance to enter the human food chain in New Zealand, no lesser standards should be permitted.

Signed,

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¹ Abbreviations: EMEA, European Agency for the Evaluation of Medical Products; USFDA, United States Food and Drug Administration