Board for Gene Technology
January 18th 2019

Statements of the supervisory Authorities for Gene Technology Act on the implementation of ECJ ruling on new mutagenesis techniques

The Finnish supervisory authorities for the Gene Technology Act (377/1995) provided the following statements when the Board for Gene Technology requested about the use of novel mutagenesis techniques (NMTs) in Finland and the implementation and effects of the ECJ ruling on NMTs.

(Unofficial courtesy translation.)

Finnish Food Authority:

Finnish Food Authority is not aware that NMTs would be used in food or feed production in Finland. Food and feed industry uses ingredients produced by GMMs, e.g. vitamins, but as the legislation does not require labeling, GM monitoring is not possible. Moreover, in the absence of methods, analytical control is not possible. The importers and the supervising authority have to rely on document information, which cannot be confirmed by analyses. In the Member States, import from third countries is based on approval of establishments in third countries by the European Commission, and from such establishments GMM products can be imported into Europe. Consequently, the supervisory authority may check whether the product has been manufactured in an establishment approved by the European Commission.

As far as Finnish Food Authority knows, commercial Finnish plant breeders do not use NMTs for breeding. However, many plant varieties from foreign breeders are accepted in the Finnish catalogue of varieties. Finnish Food Authority has no knowledge of the use of NMTs in them. While the use of traditional genetic modification methods should be indicated in the application for acceptance on the variety list and their use can be retrieved retrospectively, this is not possible with NMTs. Therefore, it is necessary to trust the applicant to make a notification of the method used.

Finnish Food Authority is not aware that NMTs are used in Finland for animal breeding. Finnish Food Authority will monitor animals imported from non-EU countries by veterinary border control. In the internal market, there are no regular controls on animals that are traded or processed. Action will be taken when suspicions arise. Guidance should be provided for traders and animal owners.

Finnish Food Authority sees that since the detection of organisms produced by NMTs is practically impossible by analytical means, official controls or self-monitoring by operators cannot be performed in practice. Mere document-based controls pose compliant and non-compliant actors in a very unequal position, which can have serious consequences for the competitiveness of the players. Moreover, limiting the use of NMTs within the EU places European plant breeders in a disadvantageous position in relation to operators in other countries. In the EU, the approval procedure for GMOs is slow, which is unfavorable for plant breeders or other users of new technologies. According to Finnish Food Authority, it is most important to assess the safety of new products on the basis of the product's characteristics, not based on the technology used.

The organisms produced by NMTs can in practice be detected analytically only by genomic sequencing. Finnish Food Authority has the potential for both Sanger and whole genome sequencing. The target genes modified by NMTs may sometimes be the same as those previously used for conventional gene transfer. In these cases, a targeted search for a mutation by sequencing could be the-

oretically possible. However, even if the mutated site is detected, finding out how the mutation has occurred - naturally or with various chemical or irradiation-induced or targeted mutagenesis methods - is virtually impossible.

An additional problem is that the food and feed analyzed contain several ingredients. Each of them should be sequenced in its entirety and compared to the genomic databases, which are not complete even for crop plants. Since each variety differs from the genome of other varieties of the same species, there should also be a genomic database for each variety. Given that the amount of target genes, species and varieties increases as a result of NMT use, detection of GMOs produced by new mutagenesis methods and not approved in the EU is therefore virtually impossible.

From the control point of view, the amount of GM material in GMOs approved in the EU is also crucial. If food/feed contains an GM ingredient produced by NMTs and approved in the EU, but the food/feed is not labeled as GM material, the amount of GM material should be analyzed so that the control authority can make a decision on labeling on the basis of the analysis results. If conventional quantitative real-time PCR (QPCR) cannot be used for analysis, it is virtually impossible to analyze the amount of GM material. Whole genome sequencing is considerably more expensive than today's common Q-PCR used to analyze GMOs, and the resources for such an analysis are limited.

Finnish Food Authority considers that while ECJ ruling as unambiguous, it does not take into account that the control authorities should have a possibility to carry out their supervision task. Supervision is carried out both in written documents and by taking samples and analyzing them. If there is no adequate documentation and/or analytical controls cannot be performed in the absence of any methodology or because of their costs, this effectively prevents effective enforcement.

Finnish Environment Institute SYKE:

Finnish Environment Institute SYKE is not aware that any NMT applications would be currently under development for the purpose of release in the environment nor of situations where they may be exposed to the environment, e.g. during waste disposal. SYKE is of the opinion that based on current information, the requirements of Annex II to Directive 2001/18/EC are sufficient to the environmental risk assessment of organisms produced by NMTs. However, in the future, situations may arise whereby the requirements should be re-examined.

SYKE does not see reason to focus its supervisory activities at this point to any NMT applications. If the use of NMTs becomes more common, SYKE's supervisory obligations will increase and additional resources are needed. SYKE does not have technical capability to detect and identify NMT organisms. SYKE does not carry out independent development work for the detection methods for supervision purposes, but relies on collaboration with other authorities, such as Customs and Finnish Food Authority. SYKE states that once the operator has provided legitimate information on the application of NMTs, controls are carried out on the same principles as for the conventional GMOs.

National Supervisory Authority for Welfare and Health (Valvira):

Valvira is not aware of NMT microorganisms to be developed with the purpose of release in the environment, or of situations where they may end up in the environment, e.g. during waste disposal.

However, it is aware of contained use of NMT microorganisms for other purposes. The same protective and isolation measures are used as when using conventional GMOs belonging to the corresponding risk class. Information on the use of NMTs has come to Valvira's knowledge in the context of its regular GMO supervision activities.

Valvira states that NMT organisms have not been reported to cause new types of unintended health effects for humans in comparison with organisms modified with conventional mutagenesis. Unless foreign heritable material is not introduced in the target cell, the changes produced by NMTs are related to different degrees of activation/inactivation of the cell's own functions as a result of point mutations, deletions and insertions, as also in traditional mutagenesis. It is extremely unlikely that an adverse property would arise solely as a result of a mutation in the organism's own genome unless the genome already contains sequences whose inactivation or activation might result in the expression of a harmful trait. Yet, it cannot be completely excluded that a mutation would affect the nature of a function, e.g. the substrate specificity of an enzyme. However, the possible health effects of mutagenesis are not resulting from the mutagenesis method used, but from the function of the mutated sequence in the cell. Thus, the probability of health effects depends on the nature of the mutated functions, e.g. presence of sequences encoding toxins or harmful metabolites. By using a template different from the genome sequence of the target organism, new traits and (depending on the new trait) new health effects can be introduced which are not possible using conventional mutagenesis.

Gene editing of crop plants can potentially lead to large-scale exposure of humans and farm animals to the gene edited organisms, and hence it is essential to identify potentially harmful health effects of their food and feed use. However, when gene editing is applied to conventional crop plants which have a long breeding history, unintentional toxic or otherwise detrimental effects on health are very unlikely. Food safety can therefore be ensured by the same means as for food plants modified with traditional mutagenesis methods. This applies also to gene editing of farm animals.

At present, the focus of gene editing is in the therapeutic use of edited cells, which does not cause population-level health risks. So far, the clinical and preclinical trials of GM organisms in general have been performed as contained use.

Valvira would prioritize monitoring the use of gene editing in poorly characterized organisms with a short history of use, as well as in organisms with toxic, pathogenic or detrimental properties. Special attention should be based on large-scale use of organisms with a short history of use e.g. as production platforms.

Regular GMO monitoring methods can be used when the user has notified the use of gene editing for deliberate release, as the notifier must present the detection and identification methods for the organism in the B-notification. Illegal use can be supervised by direct requests of information for the relevant operators as well as by following new products to be launched on the market and by making more detailed studies on whether their properties might arise from NMTs. Such properties could include e.g. disease resistance, rapid growth, shortened generation time, or phenotypic changes (taste, color, shelf life).

According to Valvira, extending the scope the GMO regulation to gene editing requires new supervising practices and thus extra resources. Their extent depends on how widely NMTs will be used in and outside EU. Gene editing may not be regulated in all countries of import, which has to be taken into account in controls. Also, more users will start using gene editing as the methods become

easier and cheaper. Some of them may neglect the notification requirements, especially as it may not be possible to unquestionably prove the use of gene editing. Crop research will probably move outside the EU to countries which are not regulating gene editing extensively. On the other hand, introduction of new technologies in itself could make plant breeding for the Finnish climate economically viable, potentially starting GM plant cultivation in Finland. Gene editing can also be an economically viable way to modify a number of sites in the genome, so the range of properties to be modified is likely to expand. NMTs also allow modifying such prokaryotes or eukaryotes (including eukaryotic microbes) for which effective molecular biology tools have been lacking. Supervision must be prepared for a much wider range of both species, applications and users.

For the time being, Valvira has not used laboratory analyses to control the use of GMOs or their spread into the environment, and Valvira does not have its own analytics service. If needed, the analytical services will be obtained from external actors on a case-by-case basis. When the modifications made with NMTs do not differ from those induced by traditional mutagenesis or from natural mutations, there is no laboratory analysis method to undeniably demonstrate the use of gene editing technology.

For the detection of the organisms which have been notified, the methods described in the application can be used. On suspected unauthorized use, the operator would be requested information on the origin of the organism, its characteristics and the genetic material affecting the phenotype, as well as on possible risk assessments and authorizations. Based on these documents, available sequence data and with other scientific knowledge Valvira would evaluate the safety, possible use of NMTs and the need for a risk assessment, as specified in the GMO or other legislation. Consultation of experts for the analyses and interpretation of their results would be needed case-by-case. The authorities should work together to find out what kind of information is already collected under the existing regulatory frameworks on the deliberate release of organisms for which NMTs may be used.

The ECJ decision does not indicate whether it also applies to the contained use of NMT organisms. If contained use of NMTs is out of scope of GMO legislation, which criteria should be fulfilled to verify that it is not question of deliberate release? And how should the supervisory authority control that NMT organisms have not been disseminated to the environment from contained use?