21 May 2015

Non Paper

On the regulatory status of plants generated by oligonucleotide-directed mutagenesis (ODM):

A) Reasoning:

The following arguments lead to the conclusion that organisms generated by ODM are not within the scope of the GMO legislation:

i. ODM is a technique/ method of genetic modification in the meaning of Art. 2 (2) of Directive 2001/18/EC. However, it yields organisms that are excluded from the Directive in accordance with **Annex I B** (1). The mode of action of the oligonucleotide molecule is comparable with that of a chemical mutagen, introducing point mutations of one nucleotide at a specific locus into the plant genome. It is impossible to differentiate between these i.e.: the point mutations caused by ODM and point mutations that are caused by natural mutagenesis or chemical mutagenesis. Mutations induced by mutagenesis are not regarded as genetic modifications according to Annex I B (1) of Directive 2001/18/EC.

ii. In excluding the organisms, in accordance with Annex I B, the following have been taken into consideration:

1. Meaning of recital 17 of Directive 2001/18/EC
   Recital 17 refers to **certain techniques** of genetic modifications that have been conventionally used and have a long safety record. Mutagenesis is such a technique. **ODM is a variation of mutagenesis**. Therefore, ODM is exempted. Annex I B (1) does not differentiate between variations of the "technique/method mutagenesis". Furthermore, the recital only serves as an interpretation of the Directive and does not have the quality of a legal norm. New technical developments shall be examined case-by-case whether they fall under the Directive or not.
   In addition, Recital 17 cannot be used as a converse argument to exclude techniques without 'conventional use' and without a 'long safety record' from being part of the list in Annex I B (1). When reversed, the sentence stands as "The directive should apply

to organisms obtained through certain techniques of genetic modification which have not been used conventionally in a number of applications and which do not have a long safety record." It follows, that all techniques of genetic modification developed after 2001 would result in the production of GMOs. If this were true, there would be no need for a definition of GMO as given in Art. 2 Nr. 2 in conjunction with Annex I A and also not for the exception in Art. 3 of Directive 2001/18/EC. Additionally, the distinction between Annex I A and Annex I B would be unnecessary.

2. No involvement of recombinant nucleic acid molecules

There is no explicit definition of 'recombinant nucleic acid molecules' in Directive 2001/18/EC. Annex I A, part 1 (1) provides the only insight. It sets out three criteria: i.e. techniques involving recombinant nucleic acid involve (i) the formation of new combinations of genetic material, (ii) the incorporation of nucleic acid molecules produced outside the organism (via a vector) and their (iii) continued propagation. The use of the template oligomer in ODM does not meet any of these criteria.

- Irrespective of what is or is not stated in the Directive it is difficult to argue that the oligomer is a recombinant nucleic acid molecule. DNA fragments from two or more sources **are not reassembled** to form a new (recombinant) molecule. The template oligomer is identical to an endogenous plant DNA fragment with the exception of one nucleotide. Single point mutations occur naturally and DNA with a single base pair change is not considered recombinant.
- The template oligomer used in ODM often contains **chemical modifications**. Due to these modifications it is, in such a case, not a recombinant nucleic acid molecule. It is questionable whether such a modified molecule can be considered a nucleic acid molecule at all.
- ODM does **not use integrative vector systems** (virus, bacterial plasmid or other) in the meaning of Annex I A, part 1 (1) of Directive 2001/18/EC. An integration of new combinations of genetic material into the plant genome does not occur.
- The transiently introduced, chemically synthesized and modified oligonucleotide does **not represent heritable material produced** outside the cell in the meaning of Annex I A, part 1 (2) of Directive 2001/18/EC. The oligonucleotide is also **not capable of continued propagation** (Annex I A, part 1 (1)). This is because it cannot replicate or be transcribed in the cell.

3. Less risk implications

The reason for implementing gene technology regulation in the EU was a concern about gene combinations that are highly unlikely in the nature (recombinant technology in the meaning of using enzymes to link together large segments of DNA of very different origins). This is not true with single **nucleotide mutations** since they **are ubiquitous in nature**. ODM is **a more precise way**[1] of producing favored mutations than radiation or chemical mutagenesis because ODM produces far less non favored off-targets. Therefore, it is **less risk associated** compared to radiation or chemical mutagenesis. Radiation and chemical mutagenesis, however, are excluded from the legislation.

4. Non applicability of the precautionary principle

The **precautionary principle** applies to cases of scientific uncertainty. Here, the uncertainty is not pertaining to science but, if at all, to the interpretation of the law. The question of whether plants generated by ODM create a risk to human health and the environment similar to GMOs is not at issue because of the reasoning given in A) ii. 3.

B) Consequences, if ODM produced plants deemed to be GMO:

B1. One of the principles of the EU-law on genetic modification is that genetic modifications can be detected and identified in the GM plant or GM animal (e.g. GM maize, GM soybean). Authorization in the meaning of Art. 4 (2) Regulation (EC) No 1829/2003, therefore, requests in Art. 5 (3) methods of detection, sampling and identification of the transformation event. However, **methods allowing the detection of point mutations do not permit the unambiguous identification of ODM plants**. This is because the detection method is able to identify the sequence variation but not the technique applied to introduce a point mutation (irradiation, chemicals, ODM). In addition, it is questionable if quantification of a single mutation in a pool of unmodified DNA is feasible in order to comply with the requirement for official control of the 0.9% labeling threshold. It is thus highly questionable whether such "ODM-GMO" could be authorized, if legal requirements according to Art. 5 (3) in conjunction with Art. 6 (3) d), 6 (5) f), 7 (2) of Regulation (EC) No 1829/2003, Art. 3 e) and Annex I of Regulation (EC) No 641/2004 and Art. 8 of **Commission Implementing**

[1] This attribute provides a higher level of safety in view to recital (5) and Article 4 of Directive 2001/18/EC

Regulation (EU) No 503/2013 cannot be fulfilled. There might be also a legal need for conventional breeders to prove that their "traditionally" mutated varieties were not created by ODM.

B2. How could the zero tolerance policy of the EU be maintained for products generated by ODM? For example, it would **not be possible to identify small impurities of "ODM-GMOs"** in conventional seeds regardless of whether the "ODM-GMOs" are authorized or not. As a consequence, especially imports could not be reliably controlled. In addition, bureaucratic burdens for public administration and private business would increase tremendously and would be in contravention of the EU's Better Regulation Principles..

B3. Green, red and white biotechnologies are using this technology. The **decision on ODM has greatest impact on medical research and industrial biotechnology**, as the contained uses of GM plants, animals and microorganisms are all affected as well.

B4. The classification of plants generated by ODM as GMOs would lead to **disproportionate legal requirements** for the authorization of these plants and products derived from them in comparison with similar or even identical organisms resulting from traditional mutagenesis, which actually involve higher risks than ODM. The **financial burden for Small and Medium Enterprises** (SMEs) using "ODM-GMO" would become too high so that de facto only a few big companies might be able to use this technology.

B5. There is a high risk that the EU falls further behind other countries (e.g. China, USA) with respect to research and development of new technologies, should plants generated by ODM be classified as GMOs, because this would entail a **"chilling effect"** reaching far beyond ODM. The political guidelines for the new Commission of July 2014 conclude that the EU needs to **stimulate investment in new technologies** and to ease access to markets and to finance, **particularly for SMEs**, in order to create jobs and economic growth.