Reports of Cases

OPINION OF ADVOCATE GENERAL
SZPUNAR
delivered on 27 October 2022[1]

Case C-688/21

Confédération paysanne,
Réseau Semences Paysannes,
Les Amis de la Terre France,
Collectif Vigilance OGM et Pesticides 16,
Vigilance OG2M,
CSFV 49,
OGM: dangers,
Vigilance OGM 33
v
Premier ministre,
Ministre de l'Agriculture et de l'Alimentation,
intervener:
Fédération française des producteurs d'oléagineux et de protéagineux

(Request for a preliminary ruling from the Conseil d'État (Council of State, France))

(Reference for a preliminary ruling – Environment – Deliberate release of genetically modified organisms – Directive 2001/18/EC – Article 3(1) – Scope – Point 1 of Annex I B – Mutagenesis – Exclusion – Techniques of *in vitro* random mutagenesis – Techniques/methods of genetic modification which have been conventionally used and have a long safety record – Protection of human health and the environment)

Introduction

1. Genetic modifications occur naturally in all living organisms. They may be triggered by endogenous factors, such as an error in the copy of DNA during the multiplication of cells, or exogenous factors, such as irradiation, inter alia, by UV rays, of the chemical agents, viruses, and so forth. Those modifications take place at the cellular level of the organism. Once they have stabilised, they may be transmitted to subsequent generations. They are then referred to as 'mutations'. Mutations favourable to the organism are promoted in the natural selection process, while those harmful to the organism are eliminated. Thus, mutations allow organisms, in particular, to adapt to changes in the environment. This process is the driving force of evolution. Technically speaking, all living organisms are therefore genetically modified.

[1] Original language: French.

2. As long ago as the Neolithic Revolution, man genetically modified plants [2] to transform wild species into species of significant nutritional interest. Virtually all plants now intended for human consumption, from wheat to bananas, are the result of deliberate artificial selection by man, of naturally occurring mutations ('spontaneous' mutations) and of the hybridisation of different varieties; they have only very little in common with their wild ancestors.

3. In the course of the 20th century man mastered the technique that enables mutations to be caused, with the help of chemical or physical factors, at a much more rapid rate (between 1 000 and 10 000 times greater) than spontaneous mutations. This technique is called 'mutagenesis'. [3] Since mutations induced in this way, as in nature, are accidental in nature, the process requires the selection of those having an agricultural interest. This process is referred to as 'random mutagenesis', also known as 'traditional mutagenesis'.

4. Applied first of all to entire plants or parts of plants (*in vivo*), random mutagenesis may also be applied to *in vitro* cultures of organs, tissues, clusters of undifferentiated cells (callus), isolated cells and protoplasts. [4] *In vitro* cultivation results in the regeneration of an entire plant on the basis of the plant material thus cultivated.

5. At the end of the 20th century, scientific progress made it possible to split the genome and to introduce into it one or more genes from a different organism, including from an organism which could not naturally transmit its genetic material to the host organism, such as an organism belonging to a different species. Such a process is known as 'transgenesis' or 'genetic engineering'.

6. Last, the techniques developed mainly at the beginning of the present century make it possible to cause targeted mutations, relating to a specific gene and producing the desired modifications from the outset, so that there is then no need to have recourse to selection. These techniques are known as 'directed mutagenesis' or 'genome editing'.

7. These new techniques of genetic modification, in particular transgenesis, give rise, within the European Union, to strong feelings of repulsion on the part of a significant proportion of society and some farmers. The scepticism which these new techniques encounter has led to a strict legislative framework applicable to genetically modified organisms (GMOs), which in most Member States takes the form of a simple prohibition. [5]

8. The present case concerns whether the varieties resulting from *in vitro* random mutagenesis, thus far considered to be excluded from the scope of that legislation, and some of which are cultivated in the European Union, including pesticide-resistant rape varieties at issue in the main proceedings, must now come within that legislation and, most likely, share the fate of transgenic varieties.

[2] Also of animals, although that question is not the subject matter of this Opinion.

[3] It would be more accurate to speak of 'induced mutagenesis'. However, I shall use the word 'mutagenesis', as that is the expression used both in the relevant EU legislation and in the Court's case-law.

[4] Cells without walls.

[5] At present, a single transgenic variety may be cultivated in the open field within the European Union. However, it is subject to a complete or partial prohibition in 19 Member States, including France.

Legal framework

9. In the words of Article 2(2) of Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC: [6]

'For the purposes of this Directive:

…

(2) "genetically modified organism (GMO)" means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination;

Within the terms of this definition:

(a) genetic modification occurs at least through the use of the techniques listed in Annex I A, part ;

(b) the techniques listed in Annex I A, part 2, are not considered to result in genetic modification;'

10. Article 3(1) of that directive provides:

'This Directive shall not apply to organisms obtained through the techniques of genetic modification listed in Annex I B.'

11. Point 1 of Annex I B to that directive reads as follows:

'Techniques/methods of genetic modification yielding organisms to be excluded from the Directive, on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms other than those produced by one or more of the techniques/methods listed below are:

(1) mutagenesis,'

12. Pursuant to Article 5(1) of Directive (EU) 2015/1535 of the European Parliament and of the Council of 9 September 2015 laying down a procedure for the provision of information in the field of technical regulations and of rules on Information Society services: [7]

'Subject to Article 7, Member States shall immediately communicate to the Commission any draft technical regulation, except where it merely transposes the full text of an international or European standard, in which case information regarding the relevant standard shall suffice; they shall also let the Commission have a statement of the grounds which make the enactment of such a technical regulation necessary, where those grounds have not already been made clear in the draft.

…

6 OJ 2001 L 106, p. 1.

7 OJ 2015 L 241, p. 1.

The Commission shall immediately notify the other Member States of the draft technical regulation and all documents which have been forwarded to it; it may also refer this draft, for an opinion, to the Committee referred to in Article 2 of this Directive and, where appropriate, to the committee responsible for the field in question.

…'

13. Article 6(2) of that directive provides:

'Member States shall postpone:

…

– … for six months the adoption of any other draft technical regulation except for draft rules on services,

from the date of receipt by the Commission of the communication referred to in Article 5(1), if the Commission or another Member State delivers a detailed opinion, within three months of that date, to the effect that the measure envisaged may create obstacles to the free movement of goods within the internal market,

…'

The facts giving rise to the dispute, the main proceedings and the questions referred for a preliminary ruling

14. The dispute in the main proceedings is between, on the one hand, Confédération paysanne, a French agricultural union, and seven associations opposed to GMOs, and, on the other hand, the Premier ministre (Prime Minister) and the ministre de l'Agriculture et de l'Alimentation (Minister for Agriculture and Food, France), supported by the Fédération française des Producteurs d'oléagineux et de protéagineux (French Federation of oilseed and protein crop producers), a trade organisation in the vegetable oil and protein sector ('the FOP'), concerning the exclusion of certain techniques of mutagenesis from the provisions of French law governing the cultivation, marketing and use of GMOs, and the inclusion of the varieties resulting from those techniques in the French catalogue of plant varieties.

15. In its judgment of 25 July 2018, *Confédération paysanne and Others*,[8] the Court, in answer to the questions for a preliminary ruling referred by the Conseil d'État (Council of State, France), which is also the referring court in the present case, submitted in the context of the same main proceedings, held, in particular, that 'Article 3(1) of Directive 2001/18, read in conjunction with point 1 of Annex I B to that directive and in the light of recital 17 thereof, must be interpreted as meaning that only organisms obtained by means of techniques/methods of mutagenesis which have conventionally been used in a number of applications and have a long safety record are

[8] C-528/16, EU:C:2018:583; 'the judgment in *Confédération paysanne and Others*'.

excluded from the scope of that directive'.[9] It also made clear that methods or techniques[10] of mutagenesis 'which have appeared or have been mostly developed since Directive 2001/18 was adopted' must not be excluded from the scope of that directive.[11]

16. The Conseil d'État (Council of State) delivered its decision on 7 February 2020. In particular, it ordered the Prime Minister to determine, within six months following notification of that decision, by decree adopted following an opinion of the Haut Conseil des biotechnologies (High Council for Biotechnology) ('the HCB'), the restrictive list of techniques or methods of mutagenesis which have conventionally been used and have a long safety record. The Conseil d'État (Council of State) considered in that decision that both the techniques or methods of 'directed mutagenesis' or 'genome edition' and the techniques of '*in vitro* random mutagenesis' appeared or were mainly developed after the date on which Directive 2001/18 was adopted and must therefore be considered to be subject to the obligations imposed on GMOs by that directive, read in the light of the judgment in *Confédération paysanne and Others*.

17. In the context of the implementation of the order made by the decision of the Conseil d'État (Council of State) of 7 February 2020, the French Government prepared a draft decree and two draft decisions. The draft measures in question are intended to amend the national legislation by providing that, 'with the exception of *in vitro* random mutagenesis consisting in subjecting plant cells cultivated *in vitro* to chemical or physical mutagenic agents', random mutagenesis may be regarded as a traditional use, without any noted drawbacks with regard to public health or the environment'. They also provide for the removal from the official catalogue of French plant varieties of the varieties obtained by the latter technique. The draft decree in question was submitted to the HCB, whose opinion, consisting of the opinion of its Scientific Committee and the recommendation of its Economic, Ethical and Social Committee, was delivered on 7 July 2020.[12]

18. On 6 May 2020, the draft decree and the two draft decisions were notified to the European Commission pursuant to Directive 2015/1535. Following that notification, the Commission, relying on the preliminary report of 19 May 2020 of the European Food Safety Authority (EFSA), on 7 August 2020 issued a detailed opinion in which it stated, inter alia, that the removal of the varieties resulting from *in vitro* mutagenesis from the official catalogue was not justified. It considered that if the draft decree and decisions were adopted in their existing state they would in its view be incompatible with Article 3(1) of and Annex I B to Directive 2001/18, and also with Article 14 of Directive 2002/53/EC[13] and Article 14 of Directive 2002/55/EC,[14] which set out the situations in which the cancellation of the entry of a variety in the catalogue is permitted. The Commission maintains that the distinction between *in vivo* mutagenesis and *in vitro* mutagenesis is not justified either by the wording of Directive 2001/18 or by the judgment in *Confédération paysanne and Others*, or by scientific data. That detailed report is supported by eight Member States.

9 Judgment in *Confédération paysanne and Others*, second paragraph of point 1 of the operative part.

10 Directive 2001/18 does not seem to distinguish between 'techniques' and 'methods' with respect to genetic modification. While Article 3(1) of that directive uses the word 'techniques', Annex I B to that directive uses the double word 'techniques/methods'.

11 Judgment in *Confédération paysanne and Others*, paragraph 51.

12 This opinion is available on the HCB's website.

13 Council Directive of 13 June 2002 on the common catalogue of varieties of agricultural plant species (OJ 2002 L 193, p. 1).

14 Council Directive of 13 June 2002 on the marketing of vegetable seed (OJ 2002 L 193, p. 33).

19. In view of the Commission's detailed opinion, the decree and decisions in question were not adopted. As the orders made in the referring court's decision of 7 February 2020 had thus not been complied with in spite of the expiry of the six-month time limit prescribed, the applicants in the main proceedings requested the referring court to ensure that its decision was implemented by imposing a periodic penalty. The ministre de l'Agriculture et de l'Alimentation requested the referring court to find that the government had employed all the diligence which the implementation of the orders contained in that decision entailed and not to impose a periodic penalty.

20. In the light of, on the one hand, the Commission's detailed opinion and EFSA's preliminary report and, on the other, the HCB's opinion of 7 July 2020, the Conseil d'État (Council of State) was uncertain as to the correct interpretation of Directive 2001/18 in the light of the judgment in *Confédération paysanne and Others*. It was in those circumstances that the Conseil d'État (Council of State) decided to stay the proceedings and to refer the following questions to the Court for a preliminary ruling:

'(1) Is Article 3(1) of Directive [2001/18], read in conjunction with point 1 of Annex I B to that directive and in the light of recital 17 of the directive, to be interpreted as meaning that, in order to distinguish from amongst techniques/methods of mutagenesis those techniques/methods which have conventionally been used in a number of applications and have a long safety record, within the meaning of [the judgment in *Confédération paysanne and Others*], consideration need be given only to the methods by which the mutagenic agent modifies the genetic material of the organism, or must account be taken of all the variations in the organism induced by the process used, including somaclonal variations, which may affect human health and the environment?

(2) Is Article 3(1) of Directive [2001/18], read in conjunction with point 1 of Annex I B to that directive and in the light of recital 17 of the directive, to be interpreted as meaning that, in order to determine whether a technique/method of mutagenesis has conventionally been used in a number of applications and has a long safety record, within the meaning of [the judgment in *Confédération paysanne and Others*], account need be taken only of open field cultivation of the organisms obtained using that method/technique, or may account also be taken of research work and publications that do not relate to such cultivation and, in relation to that work and those publications, is consideration to be given only to work and publications relating to risks for human health or the environment?'

21. The request for a preliminary ruling was received at the Court on 17 November 2021. The President of the Court did not grant the referring court's request to apply the expedited procedure, provided for in Article 105 of the Rules of Procedure of the Court of Justice. On the other hand, he decided, in accordance with Article 53(3) of the Rules of Procedure, that the present case should be given priority over others. Written observations were lodged by the applicants in the main proceedings, the FOP, the French Government and the Commission. Those parties also submitted oral argument at the hearing on 20 June 2022.

Analysis

22. The referring court asks two questions concerning the interpretation of Directive 2001/18 in the light of the judgment in *Confédération paysanne and Others*, the admissibility of which is called into question by the FOP. I do not share the FOP's doubts. On the other hand, it seems to

me that a simple answer to the questions as formulated would not provide the precision desired by the referring court or, in any event, would not permit a uniform application of the provisions at issue within the European Union. I shall therefore propose, in this Opinion, that the Court should go further than those questions, along the path already taken in the judgment in *Confédération paysanne and Others*.

Preliminary remarks

23. Before embarking on the substantive analysis, I consider that the following remarks are called for.

The subject matter of the dispute in the main proceedings

24. In submitting its questions for a preliminary ruling to the Court in the case that gave rise to the judgment in *Confédération paysanne and Others*, the referring court [15] had mentioned two techniques or methods of genetic modification the exclusion of which from the scope of Directive 2001/18 in its view gave rise to doubts: random mutagenesis applied *in vitro* and directed mutagenesis.

25. In the operative part of that judgment, the Court did not expressly mention any of those techniques or methods. It did consider, however, in particular, that 'the referring court is called upon to rule, in particular, on the techniques/methods of directed mutagenesis involving the use of genetic engineering' and that those techniques or methods 'have appeared or have been mostly developed since Directive 2001/18 was adopted'. [16] Then, relying on the findings of fact made by the referring court, the Court observed that 'the risks linked to the use of those new techniques/methods of mutagenesis might prove to be similar to those which result from the production and release of a GMO through transgenesis', because 'first, … the direct modification of the genetic material of an organism through mutagenesis makes it possible to obtain the same effects as the introduction of a foreign gene into that organism and, secondly, … the development of those new techniques/methods makes it possible to produce genetically modified varieties at a rate and in quantities quite unlike those resulting from the application of conventional methods of random mutagenesis'. [17]

26. Thus, there is no doubt that, on the basis of the judgment in *Confédération paysanne and Others*, directed mutagenesis is not covered by the exclusion from the scope of Directive 2001/18, in accordance with Article 3(1) of that directive, in conjunction with point 1 of Annex I B to that directive. It seems to be generally accepted, moreover, that that technique has been developed since that directive was adopted.

27. Conversely, the Court did not rule expressly on the method of random mutagenesis applied *in vitro*. In fact, it is precisely to that method that the dispute in the main proceedings relates. The draft legislation notified to the Commission by the French Government was the subject of a detailed opinion of the Commission because in the draft decree *in vitro* random mutagenesis was excluded from the list of methods which have been traditionally used, without proven harm for public health or the environment, and in the draft decisions the varieties obtained with the help

15 The same court, it will be recalled, as in the present case.

16 Judgment in *Confédération paysanne and Others* (paragraph 47).

17 Judgment in *Confédération paysanne and Others* (paragraph 48).

of that method were removed from the French catalogue of plant varieties. The delay in the adoption of those drafts caused by that detailed opinion is, in turn, the reason for the enforcement action brought before the referring court.

28. The outcome of the dispute in the main proceedings therefore depends on the answer to be given to the question whether the method of random mutagenesis applied *in vitro* must be excluded from the scope of Directive 2001/18.

Admissibility

29. The FOP maintains that the present reference for a preliminary ruling is inadmissible, in that, according to the judgment in *Confédération paysanne and Others* and in the light of the scientific information and data at the referring court's disposal, there is no reasonable doubt as regards the correct interpretation of Article 3(1) of Directive 2001/18, read in conjunction with point 1 of Annex I B to that directive. In concrete terms, according to that party, in the context of the main proceedings, those provisions must be interpreted as meaning that that directive is not applicable to *in vitro* random mutagenesis.

30. However, the diametrically opposite positions of the applicants in the main proceedings, on the one hand, and of the French Government, the FOP itself and the Commission, on the other hand, show in my view that neither the interpretation of the judgment in *Confédération paysanne and Others* nor the assessment of the scientific and factual data relating to *in vitro* random mutagenesis is as clear as the FOP suggests. I therefore take the view that reasonable doubt as to the interpretation sought by the referring court exists and that the present reference for a preliminary ruling is admissible. Conversely, as I have pointed out above, I shall propose that the questions for a preliminary ruling be reformulated, in order to provide the referring court with an answer which will be useful for the solution of the dispute pending before it. [18]

Argument of the parties

31. The applicants in the main proceedings emphasise, in the first place, the importance of the principles of legitimate expectation in the maintenance of legislation that protects health and the environment, of non-regression in relation to the protection of health and the environment and of precaution in the context of the interpretation and application of Directive 2001/18.

32. In the second place, the applicants in the main proceedings rely on the difference between *in vivo* mutagenesis and *in vitro* mutagenesis. In their submission, not only do mutagenesis agents function differently when they are applied to isolated cells or to entire plants, but *in vitro* cultivation in itself and the regeneration of the cells thus cultivated in plants lead to additional genetic modifications, called 'somaclonal variations'. Those modifications must also be taken into account in the evaluation of the impact of the *in vitro* mutagenesis method, since they entail potential risks for human health and the environment.

33. Last, in the third place, the applicants in the main proceedings claim that, with the exception of one rape variety, plants resulting from *in vitro* random mutagenesis have mostly been developed since 2001, alongside transgenic plants.

[18] See point 43 of this Opinion.

34. For their part, the FOP, the French Government and the Commission maintain opposite positions to those of the applicants in the main proceedings. In the first place, those parties emphasise, in essence, that *in vitro* cultivation is a very old and well-known technique and that it is not specifically associated with genetic modification. Its effects, including somaclonal variations, are also well known and do not entail specific risks for human health or the environment. Furthermore, *in vitro* cultivation does not alter the way in which the mutagenic agent leads to the appearance of mutations. Thus, apart from the frequency and number of mutations generated, *in vitro* random mutagenesis produces the same results as *in vivo* random mutagenesis and the distinction between them in legal terms is unfounded.

35. In the second place, those parties assert, with examples to support their argument, that of the plant varieties resulting from *in vitro* mutagenesis, those intended for human food or animal feed, like maize and rape, have been marketed since the beginning of the 1990s, that is to say, well before Directive 2001/18 was adopted.

The reformulation of the questions for a preliminary ruling

36. It is not for purely formalistic reasons that I present the positions taken and the arguments put forward by the parties. When Directive 2001/18 was drafted, the EU legislature designated one of the techniques excluded from the application of that directive by the clear, albeit perhaps insufficiently precise, concept of 'mutagenesis'. In the judgment in *Confédération paysanne and Others*, the Court restricted the scope of that exclusion, referring to recital 17 of that directive. However, that recital uses a general and not unequivocal criterion of techniques or methods of mutagenesis 'which have conventionally been used in a number of applications and have a long safety record'.[19] In that judgment, the Court added a further criterion, that of techniques or methods of mutagenesis 'which have appeared or have been mostly developed since [that directive] was adopted'.[20] The positions taken and the arguments put forward by the parties show the extent to which it is a complex matter to evaluate the safety of a technique or method of genetic modification and that there may be a number of diverging viewpoints on what on the face of it is the simple question whether that technique or method has long been in use.[21]

37. In the present case, the referring court asks the Court to continue along the path taken in the judgment in *Confédération paysanne and Others*, by supplementing the criteria developed in that judgment on two points, namely the character of the induced variations of the organism and the nature of the scientific data that should be taken into account for the purpose of assessing whether a technique or method of genetic modification has conventionally been used in a number of applications and whether it has a long safety record.

38. While those questions are relevant in the context of the assessment of the safety of a specific genetically modified organism, that is not the case in the context of the evaluation of the safety of a technique or method of genetic modification in general. As the Commission rightly observed at the hearing, those two analyses must not be confused when the scope of Directive 2001/18 is defined. Applied to a technique or method of GMO, the criteria of analysis proposed by the

[19] Judgment in *Confédération paysanne and Others*, second paragraph of point 1 of the operative part.

[20] Judgment in *Confédération paysanne and Others* (paragraph 51).

[21] See, to that effect, Opinion of Advocate General Bobek in *Confédération paysanne and Others* (C-528/16, EU:C:2018:20, points 105 and 106).

referring court, having regard to the multitude of data available, which are often contradictory, and the diverging opinions to which those data are apt to give rise, can only result in disparate and inconsistent solutions.

39. The first example of the ambiguities that may arise is already found in the decision of the Conseil d'État (Council of State) of 7 February 2020 and the draft decree which is supposed to implement that decision. According to that decision, organisms obtained with the help of *in vitro* random mutagenesis 'consisting in subjecting plant cells cultivated *in vitro* to … mutagenic agents' must be subjected to the obligations arising from Directive 2001/18. However, it is not clear whether that point must be taken as the definition by the Conseil d'État (Council of State) of *in vitro* mutagenesis, or indeed as a limitation relating solely to *in vitro* mutagenesis on isolated cells, as that technique may also be applied to other entities, such as protoplasts, calluses or tissues. However, the application of the criteria established by the Court in the judgment in *Confédération paysanne and Others* when evaluating the safety of *in vitro* mutagenesis may provide divergent results depending on the entity subjected to that cultivation, thus introducing a risk of confusion as regards the scope of Directive 2001/18. [22]

40. I therefore share the Commission's view that leaving it to the discretion of the authorities and courts of the Member States to decide which technique or method of genetic modification has been conventionally used for various applications and whether it has a long safety record, even with the help of whatever additional criteria may result from the answer to the questions referred in the present case, would necessarily undermine the uniformity of the interpretation of Directive 2001/18, and do so in its most fundamental aspect, namely its scope.

41. Furthermore, in order to arrive at the conclusion which it reached in the judgment in *Confédération paysanne and Others*, the Court was able to rely, first, on recital 17 of Directive 2001/18 [23] and, second, on the findings of fact made by the referring court, according to which 'the risks linked to the use of those new techniques/methods of [directed] mutagenesis might prove to be similar to those which result from the production and release of a GMO through transgenesis'. [24]

42. Yet neither the wording of Directive 2001/18 nor the material in the file available to the Court contains information on which the Court might base the rules which the referring court seeks to have laid down in the present case. [25] The Court would therefore be required to establish those rules *ex nihilo*, providing answers to what are not legal but scientific and factual questions.

43. I therefore suggest that the Court should remove the ambiguity caused by recital 17 of Directive 2001/18 and definitively settle the question whether *in vitro* random mutagenesis is excluded from the scope of that directive. Thus, I propose that the questions for a preliminary ruling in the present case be understood as relating, in essence, to whether Article 3(1) of Directive

[22] In their written observations, the applicants in the main proceedings refer to what are alleged to be the different effects which *in vitro* culture has on isolated cells by reference to multicellular entities cultivated *in vitro*.

[23] See paragraphs 44 to 46 of that judgment. That recital states that '[Directive 2001/18] should not apply to organisms obtained through certain techniques of genetic modification which have conventionally been used in a number of applications and have a long safety record'.

[24] See judgment in *Confédération paysanne and Others* (paragraphs 47 and 48).

[25] In particular, the two scientific reports drawn up in the context of the main proceedings (see points 46 to 56 of this Opinion), which deal with the differences and similarities between *in vivo* random mutagenesis and *in vitro* random mutagenesis, do not provide the basis for an answer to the questions as formulated by the referring court, or do so only indirectly.

2001/18, read in conjunction with point 1 of Annex I B to that directive, in the light of recital 17 thereof, must be interpreted as meaning that random mutagenesis applied *in vitro* comes under point 1 of Annex I B to that directive.

Analysis of the reformulated questions

44. I note at the outset that in my view there is no reason, either scientific or legal, to answer that question in the negative.

The conclusions drawn from the available scientific documents

45. It is apparent from the documents drawn up in the context of the legislative procedure at issue in the main proceedings that a distinction between *in vivo* mutagenesis and *in vitro* mutagenesis is irrelevant from a scientific viewpoint.

46. In the course of its examination of the draft legislation notified by France, referred to in point 17 of this Opinion, the Commission sought EFSA's opinion. The final report of the GMO Panel of EFSA was adopted on 29 September 2021. [26]

47. In the EFSA report, the GMO Panel considered that all random mutagenesis techniques may be applied both *in vivo* and *in vitro*, although the dose of the mutagenic agent or the exposure time may vary. The molecular mechanisms underlying the random induced mutagenesis [27] are the same as in the case of spontaneous mutations. As those mechanisms act at the cellular level, it makes no difference whether the mutagenic agent acts on an isolated cell or a cultivated tissue *in vitro* or indeed on part of a plant *in vivo*. For that reason, the types of mutations resulting from *in vitro* and *in vivo* random mutagenesis would also be the same. [28]

48. The EFSA report also addresses the somaclonal variations, referred to in the first question, not as a problem for the safety of random mutagenesis applied *in vitro*, but as a mechanism specific to *in vitro* culture itself which may prove advantageous in the mutagenesis process, in that it triggers additional mutations, from which the desired mutation may then be selected. The report lists other advantages of *in vitro* culture for random mutagenesis by comparison with random mutagenesis applied *in vivo*, [29] in particular the uniformity of the treatment and the greater ease with which mutations of greater interest can be selected.

49. However, those specific features of *in vitro* culture used in the context of random mutagenesis, including the appearance of the somaclonal variations, do not in any way alter the finding that the results of such mutagenesis applied *in vivo* and *in vitro* are identical. The GMO Panel concludes that the distinction between varieties resulting from *in vivo* and *in vitro* random mutagenesis is not justified, because the same mutations may be obtained by both techniques and the resulting mutants will be indistinguishable. [30]

[26] EFSA Panel on Genetically Modified Organisms, '*In vivo* and *in vitro* random mutagenesis techniques in plants', *EFSA Journal*, 2021;19(11):6611 ('the EFSA report').

[27] Namely the alteration and repair of the DNA.

[28] See conclusions of the EFSA report, p. 21.

[29] See EFSA report, p. 11.

[30] See conclusions of the EFSA report, p. 21.

50. While it is true that the questions relate not to the differences between the plants obtained, but to the differences between the methods used to obtain them, the objective of Directive 2001/18 is nonetheless not to regulate the methods of genetic modification, but to establish a procedure for authorising the release into the environment of the organisms obtained with the help of those methods. The exclusion from the scope of that directive, set out in Article 3(1) thereof, in conjunction with point 1 of Annex I B to that directive, therefore concerns not mutagenesis as such, but the organisms obtained by that method. The identity of those organisms therefore means that the differentiated treatment of the methods used to obtain them is unjustified.

51. The same conclusions are to be found in the opinion of the Scientific Committee of the HCB of 29 June 2020, issued in the context of the procedure for preparing the draft decree mentioned in point 17 of this Opinion ('the SC opinion'). [31]

52. Apart from the identity of the mutations caused by *in vivo* and *in vitro* random mutagenesis, the SC opinion states that the same types of mutations may result from *in vitro* culture without a mutagenic agent (by means of somaclonal variations), or indeed appear spontaneously in the field. That opinion gives the example of resistance to certain herbicides, a trait also present in the rape varieties whose removal from the catalogue is envisaged by the French Government in the context of the implementation of the decision of the Conseil d'État (Council of State) of 7 February 2020. In the conclusion to its opinion, the Scientific Committee states that it 'has found no biochemical differences between mutations, whether obtained spontaneously or by *in vitro* or *in vivo* random mutagenesis, in single cells or multicellular entities', and further that '[nor] are there any differences between the phenotypes resulting from these techniques'. [32] Conversely, it regrets that the draft decree submitted to it focuses, 'with no scientific basis', on the danger of a set of techniques, without addressing the impact and the potential consequences of the traits generated, irrespective of the method by which they are obtained. [33] On this last point, it should be observed that that was the choice of the EU legislature when it adopted Directive 2001/18 and that it is not possible to change it by judicial decision, either at national level or at the level of the Court.

53. As regards the timescale, the Scientific Committee of the HCB observes that induced *in vitro* mutagenesis was developed in the 1960s and 1970s, including on isolated cells from 1974, in particular on rape varieties marketed on a large scale since 1992. [34] *In vitro* selection without a mutagenic agent or combined with induced mutagenesis was used to obtain tolerance to a herbicide in the 1980s. It also notes that the common database of genetically modified species of the International Atomic Energy Agency and the Food and Agriculture Organisation of the United Nations, which is not exhaustive, as it is based on voluntary listing, lists 100 or so species produced by *in vitro* mutagenesis, half of them before 2001. [35]

[31] As regards the recommendation of the Economic, Ethical and Social Committee of the HCB, that committee had found that, overall, the draft decree in question was compatible with EU law and with the decision of the Conseil d'État (Council of State) of 7 February 2020. However, it did not analyse in detail the question whether *in vitro* random mutagenesis came under point 1 of Annex I B to Directive 2001/18 by reference to the judgment in *Confédération paysanne and Others*. It relied, rather, on point 3 of the operative part of that judgment, according to which Member States are free to subject organisms excluded from the scope of that directive to the obligations arising under that directive or to other obligations.

[32] The SC opinion, p. 7.

[33] The SC opinion, p. 6.

[34] The SC opinion, pp. 5 and 6.

[35] The SC opinion, pp. 18 and 19.

54. While the Scientific Committee of the HCB addresses the issue of somaclonal variations, it does so as a phenomenon specific to *in vitro* culture which on its own may trigger genetic or epigenetic modifications, whether or not they are associated with induced mutagenesis. The mechanism of those mutations is identical to that of mutations induced by random mutagenesis (and, moreover, to that of spontaneous modifications): it concerns multiple accidental and uncontrolled modifications, and only a subsequent selection procedure allows those having an agronomic interest to be chosen. [36]

55. On the other hand, it cannot be inferred from that passage in the SC opinion that, as the referring court infers, there are 'two opposing approaches', one, set out in the EFSA report, consisting in taking account only of the process by which the genetic material is modified, and the other, which the referring court adopts, but which it associates contextually with the SC opinion, consisting in taking account of all the effects on the organism of the process used, in particular the somaclonal variations.

56. Quite to the contrary, those two scientific documents mention the somaclonal variations and state unequivocally that those variations may occur independently of any mutagenic agent, but that the modifications which they trigger are of the same nature as those arising from induced mutagenesis and from spontaneous mutations. Generally, EFSA and the HCB conclude that the distinction between plants obtained by *in vivo* and *in vitro* mutagenesis is not justified. The premiss that there is a type of modifications specifically associated with *in vitro* random mutagenesis, the risk of which for health and the environment should be evaluated separately, on which the first question is based, and the distinction which the referring court endeavours to establish between *in vivo* random mutagenesis and *in vitro* random mutagenesis are therefore, in the light of the documents cited, without scientific basis.

57. I must further observe that the applicants in the main proceedings do not seriously dispute the conclusions set out in the HCB's opinion and the EFSA report. The expert evidence attached to their observations in the present case concentrates on proving the specific effects of *in vitro* random mutagenesis on isolated cells by comparison not only with *in vivo* random mutagenesis but also with mutagenesis applied *in vitro* on multicellular entities.

58. However, in the first place, it is not clear whether the decision of the Conseil d'État (Council of State) of 7 February 2020 and the resulting draft decree must be understood as being confined to *in vitro* random mutagenesis on isolated cells, as the concept of 'plant cells' is not precise. [37] In the second place, to make the scope of Directive 2001/18 depend not only on whether the mutagenesis was applied *in vivo* or *in vitro*, but also on whether it was applied to isolated cells or to multicellular entities seems to me to go clearly against the intention of the EU legislature when that directive was adopted. That is a fortiori so because the HCB opinion and the EFSA report, drawn up in the context of the legislative procedure at issue in the main proceedings, do not support such a distinction.

[36] 'Because the biochemical mechanisms resulting in mutations are the same for spontaneous mutations, for induced mutagenesis (both *in vivo* and *in vitro*) and for *in vitro* culture (somaclonal variations) – since each mutagen tends to cause one of the forms of spontaneous mutagenesis – the same types of genetic and phenotypic variant may be expected, whatever the approach. The choice of approach will depend on the expected rate of induced mutations, the regenerative ability of the material used *in vitro* and, above all, on the conditions/stages and ease of selection of the desired phenotype'. See summary at page 7 of the SC opinion. Somaclonal variations are dealt with in greater detail at pages 22 and 23 of that opinion.

[37] See point 39 of this Opinion.

The legal consequences

59. Just as there is no scientific justification for the distinction between *in vivo* random mutagenesis and *in vitro* random mutagenesis, there is no legal justification for treating differently the organisms obtained with the help of those two techniques.

60. Pursuant to Article 3(1) thereof, Directive 2001/18 is not to apply to organisms obtained through the *techniques of genetic modification* listed in Annex I B to that directive, namely, inter alia, 'mutagenesis'.

61. In that regard, it is clear from the SC opinion and the EFSA report that *in vivo* random mutagenesis and *in vitro* random mutagenesis are not two distinct techniques of genetic modification but the same technique, namely induced random mutagenesis, which may be applied to various types of materials, such as entire organisms or parts of organisms, tissues, calluses, cells or protoplasts: and there is nothing in the wording of Directive 2001/18, including in its recitals, to indicate that the EU legislature wished to distinguish the techniques of mutagenesis according to the material to which mutagenesis was applied.

62. Likewise, there is nothing to indicate that the EU legislature attached any significance to a technique excluded from the scope of Directive 2001/18 being associated with *in vitro* cultivation. As the Commission has rightly observed, both the technique listed in point 2 of Annex I B (cell fusion) and the techniques listed in the second part of Annex I A to that directive [38] (in particular *in vitro* fertilisation and polyploidy induction) are or may be practised *in vitro*, without that entailing a different classification from the aspect of that directive. I see no reason why the position should be different in the case of mutagenesis.

63. That conclusion is not called into question by the judgment in *Confédération paysanne and Others*. First, as I have already mentioned, [39] the Court clearly gave the impression that the new techniques of directed mutagenesis were not excluded from the scope of Directive 2001/18 under Article 3(1) of that directive. On the other hand, that judgment contains no suggestion of that type in relation to random mutagenesis applied *in vitro*. It may therefore be considered that that technique is not covered by that judgment.

64. Second, in accordance with the judgment in *Confédération paysanne and Others*, organisms obtained by means of the techniques or methods of mutagenesis which have conventionally been used in a number of various applications and have a long safety record come under point 1 of Annex I B to Directive 2001/18, unlike techniques which have appeared or have been mostly developed since that directive was adopted.

65. It follows, in particular, from the SC opinion that random mutagenesis, both *in vivo* and *in vitro*, was used in the selection of plant varieties well before 2001 and that the EU legislature could not have been unaware that that was so when Directive 2001/18 was adopted. [40] Furthermore, as the mechanisms and types of genetic modifications induced by random mutagenesis, both *in vivo* and *in vitro*, are the same, those two types of application of that technique do not differ as regards their safety, as evidenced by their long safety record, within the meaning of the judgment in *Confédération paysanne and Others*.

[38] Techniques which are not considered to entail a genetic modification.

[39] See points 24 to 27 of this Opinion.

[40] See point 53 of this Opinion.

The practical consequences

66. The SC opinion emphasises the practical difficulties in implementing any retroactive subjecting of the organisms resulting from *in vitro* random mutagenesis to the obligations arising from Directive 2001/18. According to that opinion, 'in the absence of molecular differences and given the current state of monitoring based on molecular biology techniques, it would be very complicated to trace and attribute mutations to a particular breeding technique'.[41] That observation is reflected in the conclusion of the EFSA report, according to which mutants resulting from *in vivo* and *in vitro* random mutagenesis are indistinguishable.

67. Unlike the position for techniques of directed mutagenesis, expressly referred to in the judgment in *Confédération paysanne and Others*, varieties obtained with the help of the technique of *in vitro* random mutagenesis were included in the common catalogue of plant varieties and are cultivated on the territory of the European Union. In so far as the traits characteristic of those varieties are similar to those of varieties resulting from *in vivo* random mutagenesis, indeed of spontaneous mutations, the practical application of any decisions to remove those varieties from the catalogue might prove to be problematic, as might the labelling and monitoring of the products resulting from those varieties.

68. Last, I consider it important to emphasise that the exclusion of *in vitro* random mutagenesis from the scope of Directive 2001/18 does not remove the plant varieties resulting from that technique and the cultivation of those varieties, or the products obtained from the plants belonging to those varieties, from all control. The laws on plant types and varieties, on the use of pesticides, on food safety, and so forth, continue to apply.

Proposed answer

69. In the light of the scientific, legal and practical considerations which have been set out, I propose that the answer to the questions for a preliminary ruling, as reformulated in point 43 of this Opinion, should be that Article 3(1) of Directive 2001/18, read in conjunction with point 1 of Annex I B to that directive and in the light of recital 17 thereof, must be interpreted as meaning that random mutagenesis applied *in vitro* comes under point 1 of Annex I B to that directive.

Conclusion

70. Having regard to all of the foregoing considerations, I propose that the Court should answer the questions for a preliminary ruling referred by the Conseil d'État (Council of State, France) as follows:

Article 3(1) of Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC, read in conjunction with point 1 of Annex I B to that directive and in the light of recital 17 of that directive,

must be interpreted as meaning that random mutagenesis applied *in vitro* comes under point 1 of Annex I B to that directive.

[41] The SC opinion, p. 28.