**GeneWatch UK response to EFSA's consultation on GM animals**

**March 2025**

The following is GeneWatch UK's response to the European Food Safety Authority's consultation on its 'Draft scientific opinion on new developments in biotechnology applied to animals: an assessment of the adequacy and sufficiency of current EFSA guidance for animal risk assessment'.[1] GeneWatch UK is concerned that the draft guidance attempts to significantly weaken the regulatory oversight of genetically modified (GM) animals in the EU, and thus fails to protect human and animal health, the environment, and animal welfare.

Numerous claims that parts of the existing guidance do not apply to certain techniques (including so-called New Genomic Techniques, NGTs, such as genome editing), or to certain traits, should be deleted: this undermines the legal requirements that are supposed to be being implemented, including international obligations under the Cartagena Protocol on Biosafety, and fails to take sufficient account of uncertainties, the precautionary principle, and unintended and unexpected effects.

## Abstract

Lines 21-24 and 28 to 31: The 3 comparisons with conventional breeding are incorrect, as (i) the equivalence of unintended effects due to so-called NGTs with conventional breeding has not been established; (ii) NGT animals require additional techniques (such as cloning) to be used, which cause adverse effects which are not equivalent to conventional breeding.
Lines 33 to 38: The partial updates proposed weaken rather than strengthening the guidance, the need to strengthen the guidance should be stated here (see specific comments in text).

## Keywords

## Summary

Lines 81 to 84 and 88 to 92: The 3 comparisons with conventional breeding are incorrect, as (i) the equivalence of unintended effects due to so-called NGTs with conventional breeding has not been established; (ii) NGT animals require additional techniques (such as cloning) to be used, which cause adverse effects which are not equivalent to conventional breeding. In particular, EFSA acknowledges (lines 2213-2214) that animal health and welfare (AHAW) concerns may also arise during the pre-commercial developmental stages, but fails to acknowledge that: (i) this means that applications of these techniques means that NGT animals are not equivalent to conventionally bred ones; and (ii) cloning (somatic cell nuclear transfer, SCNT) and/or other reproductive techniques are often also required during the production phase, in order to reduce in-breeding as the number of animals is scaled up (e.g., Mueller et al., 2019). As noted in Sections 1.3.2.1 (farmed mammals), 1.3.2.2 (farmed birds), 1.3.2.3 (farmed fish), 1.3.2.4 (invertebrates), all these reproductive techniques (without which GM animals cannot be produced) have adverse consequences: however, EFSA has failed to consider the consequences for its proposed AHAW and risk assessment guidance.

Lines 93-99: The partial updates proposed weaken rather than strengthening the guidance, the need to strengthen the guidance should be stated here (see specific comments in text).

## 1. Introduction

### *1.2 Interpretation of the Terms of Reference*

Lines 306-307: The report should have considered the risks and AHAW implications of the techniques used in combination, in particular gene editing techniques plus the techniques such as cloning needed both at the development and scaling up/production stage (e.g. Mueller et al., 2019). These techniques are described in Sections 1.3.2.1 (farmed mammals), 1.3.2.2 (farmed birds), 1.3.2.3 (farmed fish), 1.3.2.4 (invertebrates), but their consequences are subsequently ignored.
Lines 333-335: An example using pollinators is the creation of pesticide-resistant bees (Jayaweera et al., 2024; Warner, 2018).
Lines 394 to 398: The decision to exclude pre-commercial development stages from the animal welfare assessment is perverse: the use of technologies such as cloning causes major animal suffering and harm. A single gene edited animal typically requires hundreds (or sometimes thousands) of embryo or egg transfers, many of which result in mosaicism, miscarriages, stillbirths, deformities or early animal death (Tan et al., 2016; Kirkden & Broom, 2012; Srirattana et al., 2022; Mehravar et al., 2019; Salvesen et al., 2024). Further, the use of cloning and other technologies is not limited to the development phase. For example, a paper which uses modelling to argue that gene editing could be used to rapidly decrease the frequency of horned cattle in US dairy cattle populations, assumes that the top 1% of bulls would be gene edited and cloned in each generation (Mueller et al., 2019).

*1.3.2 Genome editing in livestock breeding programs*

This section should cite example failure rates for these techniques, and adverse impacts such as mosaicism, miscarriages, stillbirths, deformities and health problems (e.g., Tan et al., 2016; Kirkden & Broom, 2012; Srirattana et al., 2022; Mehravar et al., 2019; Salvesen et al., 2024). It should also note that the use of cloning and other reproductive technologies may not be limited to the development stage. If a desired genetic trait is recessive (requiring the inheritance of two copies of a gene) or complex (requiring the inheritance of multiple genetic changes), it is impossible to spread it rapidly though a population through sexual reproduction, as each descendant will inherit only half its genome from each parent. Even simple dominant traits (which require only a single copy of a gene to be inherited) must be bred into an animal population in a way which does not lose the other genetic characteristics of the breed which are regarded as important. An example of how repeated cloning might be used repeatedly at the commercialisation stage, to seek to create a herd of gene-edited hornless cattle, is provided by Mueller et al. (2019).
Lines 582 to 584: This correctly notes that genome editing may access variants that are either difficult or even impossible to access during conventional breeding (Kawall, 2019). However, it should be noted that this contradicts the conclusions in Section 3.1 and elsewhere that the use of genome editing is equivalent to conventional breeding (see detailed comments on Section 3.1).

*1.3.2.4 NGTs in invertebrates*

The example of pesticide-resistant bees should be included here (Jayaweera et al., 2024). Crustaceans should also be mentioned (Black et al., 2024).
Concerns about open releases of genetically modified non-native species should also be noted (Evans et al., 2019): this paper studies disease-vectors but the same issues apply to GM agricultural pests.

*1.3.3 EFSA risk assessment of animal health and welfare (AHAW)*

Line 814: "the production chain" is not defined. For the reasons outlined in response to Section 1.3.2, this should include the adverse effects on animals at the developmental stage (use of cloning or other methods) and in order to 'scale up' production for commercial use and maintain the trait in a commercial flock/herd or group of animals (which may require repeated use of cloning or other techniques).

*1.3.4 Risk assessment of gene-edited animals through different stages of commercial development*

Lines 852 to 858: and 865 to 868: EFSA is incorrect to exclude the risks for animals in the pre-commercial development stages from its assessment, since this is an integral part of applying both NGTs (new genomic techniques) and established genomic techniques (EGTs). EFSA acknowledges (lines 2213-2214) that animal health and welfare (AHAW) concerns may also arise during the pre-commercial developmental stages, but fails to acknowledge that: (i) this means that applications of these techniques means that NGT animals are not equivalent to conventionally bred ones; and (ii) cloning (and/or other reproductive techniques) are often also required during the production phase, in order to reduce in-breeding as the number of animals is scaled up (e.g., Mueller et al., 2019). As noted in Sections 1.3.2.1 (farmed mammals), 1.3.2.2 (farmed birds), 1.3.2.3 (farmed fish), 1.3.2.4 (invertebrates), all these techniques have adverse consequences: however, EFSA has failed to consider the consequences for its proposed AHAW and risk assessment guidance.

**2 Data and methodologies**

**3 Assessment**

***3.1 ToR 2 - Novel potential hazard and risk identification***

This section neglects the changes introduced by the necessary use of other techniques (such as cloning) in combination with NGTs and EGTs in breeding programmes, which can introduce a host of other unintended effects as noted in Section 1.3.2. This means that the hazards posed by NGTs and EGTs are not equivalent to conventional breeding. Further, the use of these techniques is not confined to the development stage (see, e.g. Mueller et al., 2019, which describes multiple rounds of cloning expected during commercialisation).
Lines 997 to 1012: This section neglects considerable evidence regarding unintended on-target effects (summarised in GeneWatch UK, 2003). The statement "the changes are

therefore similar to spontaneous mutations that can be introduced using conventional breeding" (line 999) and that hazards are of the same nature as those posed by conventional breeding (lines 1011-1012) are therefore incorrect. See, for example: Petri et al. (2022), Höijer et al. (2022), Park et al. (2022), Geng et al. (2022).
Lines 1014 to 1017: there is no evidence that off-target alterations cannot introduce novel hazards, nor are they predictable (Lessard et al., 2017; Schmidt et al. 2023; Wu et al., 2024; Jin et al, 2019; Carey et al., 2019; Petri et al., 2021; Höijer et al., 2022). Carlson et al. (2016) did not identify and report any off-target effects in gene edited hornless cattle, yet in 2019, the US Food and Drug Administration (FDA) found that apart from the intended edit, the whole plasmid, including a second copy of the repair template and the plasmid backbone, were integrated into the target location of both calves (Norris et al., 2019). This raised biosafety issues, since the plasmid backbone that was unintentionally integrated into the calves' genome also included genes conferring antibiotic resistance. Concerns were expressed that these genes could be taken up by bacteria present in the gastrointestinal tract or the body of the calves (Regalado, 2019). The statement that off-target mutations produce no novel hazards should therefore be deleted.
Lines 1018 to 1020 contain an incorrect claim because (i) new traits could be introduced due to the ability to access the whole genome (Kawall, 2019); (ii) traits that currently might exist in a natural form (e.g. pesticide-resistant bees due to pesticide exposure), pose different hazards when developed and sold as NGTs or EGTs on a commercial scale, as has been proposed (Jayaweera et al., 2024; Warner, 2018). In this case, the risk that management changes (additional spraying of pesticides) that accompany the introduction of the GM bee harm non-target organisms or health (c.f. herbicide-tolerant GM crops) must be considered in the risk assessment: this is a novel hazard.

*3.2.2.1 EFSA GMO and AHAW Panel (2012), Section 1 - The objectives of the different steps of the risk assessment procedure for GM animals and derived food/feed and issues to be considered*

Lines 1098-1099: The statement that "not all of the elements proposed...may be necessary" should be deleted because of the existence of unintended effects (see comments on Section 3.1).

*3.2.2.2 EFSA GMO and AHAW Panel (2012), Section 2 - Information required for risk assessment of GM animal-derived food and feed"*

Line 1125: The statement that information should "focus more explicitly on known toxicity and allergenicity" should be deleted because of the existence of unintended effects (see comments on Section 3.1).
Molecular characterisation must be sufficient to identify unintended changes (see comments to Section 1.3), which requires whole genome sequencing (WGS) due to the unpredictable nature of many of these changes.
Lines 1232, 1235, 1245, 1251: genetic instability may occur for unanticipated reasons and therefore evidence on gene stability should always be required.
Line 1249: absence of exogenous foreign DNA is not "only relevant to a subset of cases", because DNA from gene editing tools can be incorporated unintentionally.

Line 1250: Similarly, gene expression analysis should always be required, due to the likelihood of unintended changes.
Lines 1273-1276: No justification has been provided for the statement that a comparative analysis may not be needed: because of the potential for unintended effects, such an analysis is always needed.
Lines 1348-1351: Practical challenges do not remove the legal obligation to protect human and animal health.
Lines 1426-1428: Compositional analysis is always needed, due to the potential for unintended effects.
Lines 1441-1442: A more targeted approach risks missing unintended effects.
Line 1454 (Table 7): Prior identification of "no pathway to harm" is insufficient to protect human and animal health and the environment, due to potential unintended effects (see comments on Section 3.1).
Lines 1524-1527, 1537, 1612,1651: References to only performing tests on a "case by case' basis also risk missing unintended effects.
Lines 1576-1580: Allergenicity should always be investigated, due to the potential for unintended effects.
Line 1595: Assessment of adjuvanticity should always be required, due to the potential presence of unintended effects.
Lines 1611-1618: Testing should not be limited to anticipated pathways of harm, on a case-by-case basis, due to uncertainties and the potential for unanticipated effects.
Line 1651: Animal feeding trials with target animal species should not be limited to a case-by-case basis, due to the potential for unintended effects.
Lines 1660-1661: Limiting endpoints to plausible pathways to harm risks missing unintended effects and failing to protect human and animal health.
Lines 1672-1673: Exposure assessment is always necessary, in case of unanticipated hazards.

*3.2.3 EFSA GMO and AHAW Panel (2012), Part D - Assessment of animal health and welfare*

This should include the adverse effects on animals at the developmental stage (use of cloning or other methods) and in order to 'scale up' production for commercial use and maintain the trait in a commercial flock/herd or group of animals (which may require repeated use of cloning or other techniques). See comments on Sections 1.2 and 1.3.

*3.3.2.1 EFSA GMO Panel (2013) - 2.1. Different steps of the Environmental Risk Assessment*

Lines 1783-1792: It is not always possible to identify all 'pathways to harm' in advance, due to the unintended effects described in the response to Section 3.1. Therefore, the scope of the assessment should not be narrowed in advance, in the way described.
Lines 1794-1796: The example of sterility given here is not the only way in which poor efficacy could be linked to safety concerns. The text here should specifically mention other examples, particularly disease resistance, which (as the Guidance itself acknowledges) can lead to undetected reservoirs of disease in the GM animals, or to the evolution of pathogens to overcome resistance. This can potentially lead to harm to human or animal health, or to the environment.

*3.3.3.1 EFSA GMO Panel (2013) - 3.1 Receiving environments*

Lines 1817 and 1820 (Table 12):: It is not always possible to identify all 'pathways to harm' in advance, due to the unintended effects described in the response to Section 3.1. Therefore, the scope of the assessment should not be narrowed in advance, in the way described.

*3.3.3.2 EFSA GMO Panel (2013) - 3.2 Experimental environment*

Line 1883 (Table 13): It is not always possible to identify all 'pathways to harm' in advance, due to the unintended effects described in the response to Section 3.1. Therefore, the scope of the assessment should not be barrowed in advance, in the way described. The efficacy of the trait must be established for traits other than sterility, as this is not the only way in which poor efficacy could be linked to safety concerns. Other examples should be included, particularly disease resistance, which (as the Guidance itself acknowledges) can lead to undetected reservoirs of disease in the GM animals, or to the evolution of pathogens to overcome resistance. This can potentially lead to harm to human or animal health, or to the environment.

*3.3.3.5 EFSA GMO Panel (2013) - 3.5 Experimental design and statistics*

Line 1849: Difficultly in applying the requirements should not lead to the abandonment of the need to establish safety in species with long generation times.

*3.3.3.6 EFSA GMO Panel (2013) - 3.6 Long-term effects*

Line 1860 (Table 15) It is particularly important that assessment of long-term effects is not limited to those identified in advance as potential harms. Whole ecosystems could evolve as a result of the release of GM animals, including e.g. the evolution of pathogens or secondary pests.

*3.3.4.1 Persistence and invasiveness, including vertical gene transfer*

Lines 1925-1934: Undesirable traits, such as pesticide resistance, can be transferred to wild populations via vertical gene transfer. Open releases of genetically modified non-native species can also lead to the introgression of undesirable genetic traits into wild populations (Evans et al., 2019): this paper studies disease-vectors but the same issues apply to GM agricultural pests.
Line 1936 (Table 18): The table wrongly highlights situations in which persistence, invasiveness and vertical gene transfer do not need to be thoroughly assessed. This is incorrect, due to the unintended effects outlined in response to Section 3.1, and also due to concerns about how introduced traits may evolve, or other organisms (e.g. pathogens, pests) may evolve in response.

*3.3.4.2 Horizontal gene transfer*

Lines 1942-1946 and 1954 (Table 19): Concerns regarding horizonal gene transfer (HGT) are not limited to antimicrobial resistance genes (AMR). For example, HGT might transfer pesticide-resistance genes from a GM pesticide-resistant bee to pests.
Lines 1947-1951: There is no justification for the claim that loss of genetic diversity is "not an environmental risk".

*3.3.4.3 Pathogens, infections and diseases*

Lines 1964-1968 (Table 20): The proposed changes are shockingly poor and could pose serious risks to human and animal health and the environment, particularly in the case of disease-resistant traits: pathogens can create a silent reservoir of disease in a supposedly disease-resistant population of GM animals and/or pathogens can evolve in response to genetically engineered disease resistance, posing a significant risk to human or animal health or the environment. Genetic changes associated with other traits might also unintentionally result in a modified susceptibility to disease. Proposals to weaken regulatory oversight of such changes are irresponsible.

*3.3.4.4 Interaction with target organisms*

Lines 1973-1975 and Table 21: It is incorrect to state that the failure of population suppression poses only an economic harm: for example, temporary suppression of e.g. pests, can lead to a rebound and greater harm than if no intervention took place.
Line 1982 (Table 21): Hazards resulting from potential evolution of pathogens in pathogen-resistant animals should be addressed in the 'target' and 'non-target' organisms sections, as well as in the section on pathogens, because the potential implications for target and non-target species need to be understood.

*3.3.4.5 Interactions with non-target organisms (NTOs)*

Line 1992: Table 22: Hazards resulting from potential evolution of pathogens in pathogen-resistant animals should be addressed in the 'target' and 'non-target' organisms sections, as well as in the section on pathogens, because the potential implications for target and non-target species need to be understood. In addition, the ERA should not be limited to certain traits, as proposed in the Table 22, because of the many possible unintended consequences of using these techniques, outlined in the response to Section 3.1.

*3.3.4.7 Impact on human health*

Line 2012 (Table 24): It is not correct to state that these areas of risk do not need to be addressed in the ERA. There are many possible unintended consequences of using these techniques, outlined in the response to Section 3.1.

*3.3.4.8 Interactions with the abiotic environment*

Line 2019 (Table 25): It is not correct to state that these areas of risk do not need to be addressed in the ERA. There are many possible unintended consequences of using these techniques, outlined in the response to Section 3.1.

*3.3.4.9 Impacts of GM fish on biotic components and processes*

Line 2026 (Table 26): It is not correct to state that these areas of risk do not need to be addressed in the ERA. There are many possible unintended consequences of using these techniques, outlined in the response to Section 3.1.

*3.3.4.10 Impacts of GM mammals and birds on non-GM animal health and welfare*

Lines 1898-1905: Risk assessment should not stop at the stage of hazard identification for any GM animal. Unintended effects mean that GM animals are not equivalent to conventionally-bred ones (see response to Section 3.1).

*3.3.5 EFSA GMO Panel (2013) – 5 Post-market Environmental Monitoring*

Line 2059 (Table 28) and 2028 (Table 29): Case-specific monitoring and general surveillance should not be restricted to limited hypotheses: there are many possible unintended consequences of using these techniques, outlined in the response to Section 3.1. Animals genetically modified for sterility can potentially suppress wild populations (including intentional attempts to suppress pests or invasive species): the environmental consequences of such releases should not be excluded from the general monitoring requirements.

***4.1 ToR 4 - Specific areas and aspects of the EFSA guidance (EFSA GMO and AHAW Panel, 2012) which should be updated, adapted or complemented***

Lines 2146-2147: For the reasons outlined in Section 3.1, the use of genome editing techniques does not result in genetic changes that are "of the same nature" as conventional breeding.
Lines 2155-2156: Off-target events "should be" (not "could be") screened out before regulatory approval is sought.
Line 2173-2175 and 2182-2183: Restricting toxicological and allergenicity assessments and feeding trials on a case-by-case basis is unacceptable, as unintended changes (as outlined in response to Section 3.1) could lead to harms, which might not be identified if a full assessment is not performed.
Lines 2212-2215: Harms cause to animal welfare through cloning and other reproductive technologies used in the development of the GM animals must be included in the animal health and welfare (AHAW) assessment, as these are an integral part of the creation of the GM animal, may give rise to unintended effects as well as direct harm, and can occur throughout the process of scaling-up and marketing a flock or herd of animals (see response to Section 3.1).
Lines 2268-2270: As noted in line 1795, efficacy should be assessed where poor efficacy leads to safety concerns (for health or environment): this is not limited to sterility traits but includes other traits, e.g. disease-resistant traits (including long-term effectiveness of such traits).
Lines 2271-2291: Repeated claims that certain aspects of the current guidance should "only" be applied in certain (limited) cases should be deleted. This is because uncertainties and

unexpected effects need to be assessed. This is particularly important because of the wide range of unexpected effects that can occur, see comments on Section 3.1.
Lines 2296-2301: Case-specific monitoring and general surveillance should not be limited or waived in specific circumstances, for the reasons cited above.

### *4.2 ToR 4 - Specific areas and aspects of the EFSA guidance (EFSA GMO Panel, 2013) which should be updated, adapted or complemented*

Lines 2232-2234 and 2240-2242: It is not correct to state that the next steps are only needed if a plausible hazard is identified, or that they should be limited to certain phenotypes, as there are many uncertainties and unintended effects.
Lines 2254-2255: Assessment of long-term effects must be broad enough to encompass uncertainties and unintended effects: thus, the scope should not be restricted to pre-identified potential harms.
Lines 2268-2270: Failure of other traits (not just sterility), e.g. pathogen-resistance, can lead to potential harms, so sterility is not the only trait for which efficacy needs to be confirmed.

## 5 Overall conclusions

Lines 2313-2315 and 2320-2322: The comparisons with conventional breeding, leading to the conclusion of "no novel hazards" are incorrect, as (i) the equivalence of unintended effects due to so-called NGTs with conventional breeding has not been established; (ii) NGT animals require additional techniques (such as cloning) to be used, which cause adverse effects which are not equivalent to conventional breeding.
Lines 2325-2330: The partial updates proposed weaken rather than strengthening the guidance, the need to strengthen the guidance should be stated here (see specific comments in text above). Numerous claims that parts of the existing guidance do not apply to certain techniques or traits should be deleted: this undermines the legal requirements that are supposed to be being implemented, including international obligations under the Cartagena Protocol on Biosafety, and fails to take sufficient account of uncertainties, the precautionary principle, and unintended and unexpected effects.

## 6 Recommendations

[Will be developed by EFSA later]

## 7 References

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