Revision of risk assessment study "Application of Annex 1 of decision CP-9/13 to living modified organisms containing engineered gene drives" after the online forum.

Observation	Post Number related to observation	Actions taken
The scope of the study and definition of "engineered gene drive" should be clarified.	10117, 10118, 10119, 10122, 10127, 10129, 10134, 10139, 10145, 10162, 10170, 10178, 10183, 10184, 10193, 10203, 10207, 10215, 10225	Scope stated more clearly. Footnote added to section 1, the first paragraph of section 3, further clarification added to beginning of section 3 and section 4. The definition of "gene drive" (adapted in section 3) was referenced from the following sources: NASEM (2016), ZKBS (2016), RIVM (2016), Australian Academy of Science (2017), NEPAD (2018) and OGTR (2019). .
Extrapolation of a few engineered gene drive systems may lead to incorrect conclusions regarding all engineered gene drives.	10117, 10118, 10119, 10161	A new paragraph has been added to the executive summary and section 4 (Considerations for risk assessment) for managing considerations. Additionally, clarifying example given in Section 4.3.1 and Annex 4 (3.1).
The study could further detail horizontal gene transfer.	10117, 10118, 10134, 10191, 10225	No action taken. Gene flow is mentioned under sub-heading (i) in the Executive summary, section 4.3.2, section 4.5, section 5.1.1 (a) and Annex 4 (3.2, 5).
Little information regarding the benefits of engineered gene drives was provided and the maximum acceptable risk for the technology should be added to the study.	10119, 10128, 10170, 10178, 10182, 10189, 10221, 10223	Text added to the introduction of Section 4 to clarify that maximum acceptable risk is beyond the scope of the study and for future considerations.

		Section 4 for also states: "While the final decision on a certain application may include a weighing of the potential benefits against the risks, this element is not included in the risk assessment methodology as such"
Suggestion for the study to have more information on the effects of removing an organism from ecosystems.	10120	Clarification text added to introduction of section 4 (Considerations for risk assessment) to make a distinction between the risk assessment methodology and the scientific knowledge to inform the risk assessment.
Suggestion to include more information on other control methods (e.g. chemical control, biological control and others) as they could be informative for the risk assessment of engineered gene drives.	10127, 10128, 10137, 10145, 10147, 10148, 10149, 10153, 10162, 10166, 10170, 10175, 10178, 10208, 10216, 10225, 10226	Section 4.1.3 indicates that risk assessment of insects with engineered gene drive systems can build on existing knowledge and experience with vector control programs using insects that do not contain gene drives (e.g. sterile insect technique (SIT); incompatible insect technique (IIT)). Section 3.2 describes non-engineered gene drive systems (e.g. *Wolbachia*), which could inform risk assessment. In addition, the following has been added to the executive summary: "…information relevant for the risk assessment can be obtained from other applications in the same species or from other

		management systems addressing similar objectives"
Selfish genetic elements could additionally be considered in the study or in an Annex.	10134, 10145, 10177, 10223, 10226	New section (4.2.4; Interaction with the organism's genome) has been added to the report to add information on selfish genetic elements.
Wolbachia systems and other biocontrol methodologies may not be comparable to LMOs containing engineered gene drives.	10159, 10162, 10166, 10168, 10175, 10191	Section 3.2 and Annex 4 (section 1.5 – Managing a stepwise approach) of the study note the systems have differences. However, a phrase has been added to make this clearer under section 3.2.
Risk assessment of LMOs containing engineered gene drives should be performed on a case-by-case basis.	10128, 10129, 10137, 10145, 10147, 10148, 10149, 10155, 10170, 10181, 10183, 10192, 10193,10207, 10208, 10210, 10221, 10223, 10225	No action taken. Case-by-case nature of risk assessment methodologies are highlighted in executive summary; sections 3.1.1, 4, 4.1.1 and 5.1.3; and Annex 4.
Study primarily focused on mosquito vector control and does not include other type of applications of engineered gene drives in other organisms. Further suggestions to specify which applications are near future.	10128, 10137, 10139, 10162, 10170, 10175, 10183, 10202, 10215	Table 5 in section 3.2 updated with more applications of engineered gene drives in other organisms.
Further description of various engineered gene drive systems should be included in the study.	10192, 10199, 10215, 10227, 10162, 10175, 10226	Table 5 has been modified to capture the status of different applications of gene drives. In addition, the study presents a brief summary of different types of gene drive systems in section 3 and Table 4, and various engineered gene drive systems are detailed in

		Annex 3 along with references.
Precautionary principle was not well considered.	10135, 10159, 10166, 10175, 10176, 10185	Further mention of the precautionary approach added to Sections 1 (Introduction), 4 (Considerations of risk assessment) and the executive summary (see footnote).
The following considerations are important for risk assessment: familiarity/experience Environmental policy goals Problem formulation Evidence Risk communication	 10127, 10137, 10170, 10227, 10175, 10191, 10226 10161, 10168, 10202, 10208, 10226 10168, 10127, 10208 10127, 10147, 10223 10174, 10183, 10206, 10210, 10223	Clarification text added to the introduction of sections 1 and 4 to indicate that the risk assessment per se, the risk assessment methodology or the evaluation of the acceptability of certain applications is outside of the scope of this study. Therefore, the study does not elaborate on the important risk assessment aspects such as environmental policy goals, problem formulation, familiarity/experience, comparators, natural gene drives and weight of evidence.
The concept of the “receiving environment” is not used accurately.	10128, 10221	The idea of the ‘receiving environment’ is covered in the executive summary and section 5.1.3. In addition, clarification language has been added to the executive summary and sections 5.1.3.
The criteria and selection of stakeholders was not indicated in the report.	10137, 10170, 10178, 10183	Text added in section 2.3 to describe criteria for selection of stakeholders.

Social, cultural, economic and ethical considerations are important.	10147, 10418, 10152, 10161, 10166, 10168, 10175, 10176, 10227	No actions taken. The issue of stakeholders participation, ethical considerations and others on decision making are important but out of the scope of the study.
Active participation of indigenous peoples and local communities should be encouraged, as well as free, prior, informed consent.	10148, 10175, 10176, 10183, 10208	No actions taken. Perspectives of indigenous peoples and local communities has been covered in sections 4.6 and 5.1.4 (e), as well as Annex 4.
Challenges that are prominent for engineered gene drives are rather of a technical nature than challenges to risk assessment framework.	10128, 10145, 10155, 10183, 10221	No actions taken. Technical challenges related to risk assessment of LMOs containing engineered gene drives have been reflected in the executive summary and in section 5.1.3
Threat of an irreversible impact at a scale exceeding the intended release.	10128, 10139, 10155, 10161, 10169, 10183, 10208, 10227	No actions taken. This is reflected in the executive summary, in sections 4.1.5, 5.1.3 (c) and 5.1.4 (e) and Annex 4 (1.5 and 3).
Modified inheritance patterns differentiate LMOs containing engineered gene drives from 'traditional' LMOs.	10155, 10167, 10183	Text in the following sections has been adjusted to provide further clarity: Executive summary, section 4.1.2 and Annex 4 (1.2).
Lack of applicability of a stepwise approach, particularly for low threshold engineered gene drives.	10155, 10166, 10169 10182, 10183, 10148	No actions taken. The stepwise approach is addressed in the Executive summary, Sections 3.2, 4.1.5, 5.1.3 (c) and Annex 4 (1.5).
Challenges of LMOs containing engineered gene drives relate to the assessment of unintended and off-target effects, as well as uncertainties.	10161, 10162, 10166, 10177, 10185, 10227	No actions taken. Off-target modifications are addressed in Executive summary, sections 4.1.2, 4.2.1, 4.2.4 and Annex 4 (1.2, 2.1). In addition,

		mention of unknown effects has been made in the executive summary and under section 5.1.1
There is a lack of data on the effects of potential impact of genetically engineered non-domesticated species in non-managed, highly complex environments across larger spatio-temporal scales.	10168, 10208	Text modified in Executive summary, section 4.1.3 and 4.1.4 and Annex 4 (1.3, 1.4). Additionally, the study mentions this in section 5.1.3.
LMOs containing engineered gene drives can have the propensity for transboundary movements.	10128, 10139, 10148, 10161, 10166	No actions taken. The potential for transboundary movement of LMOs containing engineered gene drives is addressed in the Executive summary, sections 4.5.1, 4.6.1, 5.1.1 (a) and 5.1.2 (b).
Aspects of evolution of engineered gene drive systems are not detailed.	10162, 10168, 10177, 10183, 10184, 10191, 10215	Clarifying text was added to new section 4.2.4 regarding evolutionary insights from selfish genetic elements. Previously the study covered evolutionary considerations under 4.4.1, in modeling publications references in section 5.2 and Annex 4 (4.1).
There are several guidance documents and relevant experience available, which are sufficient for performing risk assessment of LMOs containing engineered gene drives.	10128, 10149, 10155, 10164, 10170, 10174, 10178, 10183, 10189, 10203, 10207, 10221, 10226	No actions taken. Existing guidance documents are detailed in section 5.2. The study also contains relevant text in section 5.1.3.
Further capacity-building and sharing of information and experiences should be done to address technical and methodological challenges.	10118, 10147, 10148, 10149,10152, 10161, 10164, 10174, 10178, 10183, 10189, 10193, 10210	Text added to introduction of section 4. However, capacity-building was considered outside of the scope of the study.
LMOs containing engineered gene drives are systems that	10166, 10191, 10227	Text adapted in Executive Summary, section 4.1.2.

continuously modify organisms with each generation.		Coverage can also be found in section 5.1.3 (c).
The prevention of resistance evolving in engineered gene drive systems could be further elaborated on in the study.	10212	Two sentences with corresponding references (Kryou et al. 2019; Oberhofer et al. 2019) were added in section 4.4.1 and Annex 4 (section 4.1). Section 4.4.1 has been re-organized to emphasize resistance.
Comments regarding the use of relevant comparators when assessing LMOs containing engineered gene drives Natural gene drive systems could be used as comparators	10127, 10129, 10155, 10169, 10191, 10199 10127, 10137, 10155, 10216	Text was added to the introduction of section 4 to clarify that comparators were considered to be beyond the scope of the study.
Study does not acknowledge that removal of invasive species may carry risks as well.	10171, 10175	Sentence added to section 4.3 and Annex 4 (3) to reflect this observation.
Risk assessment should be a comparative exercise.	10155, 10174, 10189,	No actions taken. The comparative approach is mentioned in section 4.1.3 and Annex 4 (1.3).
Challenges of LMOs containing engineered gene drives relate to the availability of information to support risk assessment.	10139, 10148, 10155 , 10179, 10182, 10183	Clarifying text added to introduction of section 4 and 4.1.3. The study also contains relevant text in section 5.1.3 (c).
The utilization of modelling for risk assessment of LMOs containing engineered gene drives is a challenge and may have limitations.	10166, 10182, 10185, 10191, 10199	Text in sections 3 (introduction) and 5.1.3 (c) has been modified to capture this viewpoint. Section 3.2 also contains relevant text.
Modeling could be used to supplement risk assessment methodologies (e.g. address the likelihood of horizontal gene transfer, manage uncertainties)	10128, 10148,10155 10183, 10195, 10202, 10206, 10221, 10223	No actions taken. Modelling is covered in the executive summary, section 5.1.3 (c), literature references in section 5.2 and Annex 4.

For gene drive organisms, theoretical modelling exercises address the spread and functionality of specific gene drive constructs while potential ecological implications have been discussed on a theoretical level only	10155	A sentence in this regard has been added at the end of section 3.
Biodiversity should not be restricted to keystone species, valued species or ecosystem services	10199	Text modified in section 4.3 to clarify that the meaning of biodiversity is not restricted to 'keystone' species.
Lack of ecological knowledge and data on the species and ecosystems that could be affected.	10199, 10148	Clarification text added to introduction of section 4 to make a distinction between the risk assessment methodology and the scientific knowledge to inform the risk assessment, as well as text additions in section 4.3 and Annex 4 (3)
Uncertainty analyses should be done to complement risk assessment methodologies.	10187, 10206	No actions taken. Uncertainty analysis has been captured in the Executive summary, section 4.1.5 and 5.1.3 (c).
Selfish genetic elements could provide insights on how engineered gene drives could evolve and or on new applications.	10207, 10226	Text in new section 4.2.4 captures this observation.
Monitoring programmes are important for releases of LMOs containing engineered gene drives	10148, 10183, 10195, 10199, 10208, 10223	Text has been added to the introduction of section 4 to clarify that considerations for risk assessment, such as monitoring, were beyond the scope of the study and therefore not detailed. Monitoring with respect to Wolbachia systems is mentioned in section 3.2.

Risk management aspects are important for LMOs containing engineered gene drives.	10148, 10159, 10169, 10191, 10208, 10212, 10215	The introduction of section 4 has been adapted to clarify the considerations for risk assessment. However, the study does not detail risk management and mitigation practices.
The study could have further detailed confinement and security measures.	10148, 10212	Additional sentence added to section 3.2. . Confinement mentioned in executive summary, section 3.2, section 4.1.5, section 5.1.4 (e), section 5.2 and Annex 4 (1.5)
Suggestion to include information on ecological niche filling and vector switching.	10162, 10175, 10212, 10225	No action taken. Niche replacement and vector considerations are found in sections 4.3.2, 4.3.3 and 4.3.4, as well as in Annex 4 (3.2, 3.3 and 3.4).
Insufficient information regarding the literature search; correction provided of type of search performed.	10127, 10167, 10178, 10207	Wording “systematic review” replaced with “literature review” in title of section 2.1 and Annex 1.
Example of EFSA consultations on modified insects containing synthetically engineered gene drives was provided as a relevant event.	10127	Text added to section 5.2 (Information on stock-taking exercise related to existing guidance).
Differentiation should be made between cargo and driver in engineered gene drive systems.	10226	Clarification text added to executive summary. The study covers cargo-drive linkage in section 4.2.2, section 5.2 (modeling publication) and Annex (2.2).
List of references shared as a complement to the list of references consulted during the study.	10222	List of reference has been cross-checked and relevant publications have been included in the study.
An English language version of a French national opinion	10225	Specific reference to both languages appears in

document related to LMOs containing engineered gene drives was shared.		section 5.2 and URL for both languages included in reference list.
Biology document for *Aedes aegypti* mosquitoes was provided to supplement the study.	10182	The document is now referenced in sections 4.1.3 (Targeting non-domesticated species) and Annex 4 (section 1.3 – Targeting non-domesticated species).
Additional reference provided for recent report on LMOs containing engineered gene drives was shared to complement the study.	10162, 10177	ENSSER-DW 2019 report now included as footnote in section 2.2.3 and in reference list.
Recent report on LMOs containing engineered gene drives and additional literature were shared to supplement the study.	10135	URL to RAGES 2020 report included as footnote in section 2.2.3.
Additional reference regarding near future engineered gene drive systems provided to complement the study.	10149	Publication now included in the reference list and cited in the introduction to section 3.
Terminology for various engineered gene drive systems may not be clear and/or inaccurate.	10187, 10225, 10227	Footnotes and references have been added to the study to prevent confusion regarding terminology used to describe engineered gene drive systems (see section 3 and Table 4).
Risk assessment frameworks are not limited to domesticated species and managed environments. LMOs without engineered gene drives can spread into non-managed environments or be of non-domesticated species	10129, 10155, 10167, 10183	Text modified in section 4.1.3, section 4.1.4, section 5.1.3 (c), and Annex 4 (1.3 and 1.4). For example, Section 4.1.3 states “these challenges are not unique for gene drives and will be faced by any application in a non-domesticated species”.