

Title

Summary of the Literature Review for A2704-12 Soybean
October 1, 2018 – September 30, 2019

Final Report

Data or Guideline Requirement

Explanatory note on literature searching
conducted in the context of GMO applications for (renewed) market authorization
and annual post-market environmental monitoring reports on GMOs authorised in the EU market.
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Report No: 19-RSSB0015
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October 1, 2018 – September 30, 2019
Page 2 of 32

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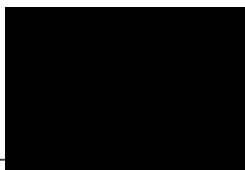
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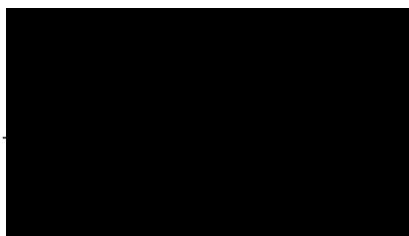


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Report No: 19-RSSB0015
Summary of the Literature Review for A2704-12 Soybean
October 1, 2018 – September 30, 2019
Page 3 of 32

SIGNATURE PAGE

Principal author:



Date

2019-11-29

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Report	[REDACTED] [REDACTED] [REDACTED]

TABLE OF CONTENTS

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS	2
SIGNATURE PAGE	3
Study Personnel	4
TABLE OF CONTENTS	5
TABLES	6
Appendices	6
SUMMARY	7
1. INTRODUCTION	8
2. OVERALL METHODS	8
2.1. Objective of the scoping review	8
2.2. Review questions	8
2.3. Criteria for relevance	9
2.4. Reference publication	12
3. SEARCH METHODS AND OUTCOMES	12
3.1. Time window and date of the literature search	12
3.2. Search strategy	12
3.3. Databases used in the literature search	14
4. MANUAL SEARCHES	15
4.1. Manual searches of web pages of food safety, agriculture, and biotechnology-related authority webpages	15
4.2. Manual searches of reference lists of recent review articles	16
5. RESULTS OF THE STUDY IDENTIFICATION AND SELECTION PROCESS	19
5.1. Screening of titles and abstracts to exclude obviously irrelevant references (Stage 1) ...	19
5.2. Detailed assessment of eligible references (Stage 2)	20
6. NARRATIVE SYNTHESIS AND SUMMARY OF RELEVANT STUDIES	29
7. CONCLUSION	29
8. REFERENCES	29
9. APPENDICES	30

TABLES

Table 1:	Eligibility/inclusion criteria to establish the relevance of retrieved publications	9
Table 2:	Search profile for database search.....	13
Table 3:	Overview of the selected databases and summary of search results from each database	14
Table 4:	Search of websites for regulatory authorities for food and feed safety, agriculture, and biotechnology	15
Table 5:	Documents for which reference lists were scanned for relevant studies	17
Table 6:	Results of the publication selection process	20
Table 7:	Report of all relevant publications retrieved after detailed assessment of full-text documents for relevance: ordered by category of information/data requirement(s)	21
Table 8:	Report of publications excluded from the risk assessment after detailed assessment of full-text documents	21
Table 9:	Report of unobtainable/unclear publications	28
Table 10:	Summary of all relevant publications retrieved after detailed assessment of full-text documents for relevance(Stage 2): ordered by category of information/data requirement(s)	29
Table 11:	Report of the reliability and implications for the risk assessment of all relevant publications retrieved after detailed assessment of full-text documents for relevance(Stage 2): ordered by category of information/data requirement(s)	29

APPENDICES

Appendix 1	Search history	30
Appendix 2	Database descriptions	31

SUMMARY

A2704-12 *Glycine max* was transformed by direct gene transfer using vector pB2/35S Δ CK, which carries a phosphinothricin acetyltransferase (*pat*) gene and a beta-lactamase (*bla*) gene cassette. The *pat* gene encodes the phosphinothricin acetyltransferase (PAT) enzyme and confers tolerance to glufosinate-ammonium herbicides. Prior to transformation, the vector was digested with the *Pvu*I restriction enzyme to disrupt the coding sequence of the *bla* gene and thereby removing any remote possibility of its expression. The OECD identifier is ACS-GM005-3.

A scoping review was performed for A2704-12 soybean and its newly expressed protein, PAT/*pat*. The objective was to determine if there were studies about the molecular characterization of A2704-12 soybean, its effect on food and feed safety, or on environmental safety, that might require in-depth examination. A set of broad literature searches was performed using several bibliographic databases covering scientific literature from October 1, 2018 to September 30, 2019. Additional sources of information, such as web pages of regulatory authorities for food and feed safety, agriculture, and biotechnology were searched for the same time window, along with the bibliographies of relevant reviews. The references identified were evaluated for potential relevance to the scoping review questions according to pre-defined criteria.

The literature searches identified a total of 123 unique publications, which were subject to rapid assessment to exclude obviously irrelevant publications. A total of 12 publications were progressed for further assessment. After a detailed review, all 12 publications were determined to be not relevant.

No publications were found that contained new data on the molecular characterization of A2704-12 soybean and its newly expressed protein, PAT/*pat*. Similarly, no new publications were found that suggested any potential adverse effects of this event on human and animal health, or the environment.

In summary, the literature searches and detailed review of the retrieved publications identified no publications that would change the existing safety assessment of A2704-12 soybean.

1. INTRODUCTION

A2704-12 *Glycine max* was transformed by direct gene transfer using vector pB2/35S_{AcK}, which carries a phosphinothricin acetyltransferase (*pat*) gene and a beta-lactamase (*bla*) gene cassette. The *pat* gene encodes the phosphinothricin acetyltransferase (PAT) enzyme and confers tolerance to glufosinate-ammonium herbicides. Prior to transformation, the vector was digested with the *PvuI* restriction enzyme to disrupt the coding sequence of the *bla* gene and thereby removing any remote possibility of its expression. The OECD identifier is ACS-GMØØ5-3.

The objective of the literature searches described here was to determine if there were publications published between October 1, 2018 and September 30, 2019 that mention the molecular characterization of the A2704-12 soybean, and/or any adverse effects of A2704-12 soybean in food, feed or the environment. In that context, broad and inclusive literature searches were performed and the articles retrieved were reviewed in a comprehensive and transparent manner. The literature review was performed as recommended in the European Food Safety Authority (EFSA) explanatory note on literature searching conducted in the context of Genetically Modified Organisms (GMO)¹ applications and post-market environmental monitoring activities (2019).

The literature searches were performed for A2704-12 soybean and its newly expressed protein PAT/*pat*. The search terms also included relevant synonyms, intended trait, plant species and general GMO terms.

2. OVERALL METHODS

2.1. Objective of the scoping review

The objective of the scoping review was to survey the evidence base for the A2704-12 soybean and the newly expressed protein PAT/*pat*, in order to identify any issues related to the molecular characterization of A2704-12 soybean, food and feed safety, or environmental safety, that may require a more detailed examination.

2.2. Review questions

Review questions were formulated to conform to PECO structure (Population, Exposure, Comparators, Outcome) if possible, and to meet data requirements. They were modeled after the review question examples provided in the EFSA 2019 explanatory note¹.

Question 1: Were any studies published during the reporting period that describe adverse effects on human or animal health or the environment of A2704-12 soybean and the PAT/*pat* protein?

Key elements:

Population: Human health; animal health; environmental safety

Exposure: A2704-12 soybean, derived food/feed products, newly expressed protein in A2704-12 soybean

Comparators: When applicable, comparable populations or subjects exposed to appropriate controls (e.g., vehicle only, innocuous control protein, non-GM comparator) or conventional counterpart used for comparative analysis of plant material

Outcome: Adverse effects

Question 2: Were any studies published during the reporting period that focus on the molecular characterization of A2704-12 soybean and the PAT/*pat* protein?

Key elements:

Population: A2704-12 soybean and newly expressed protein in A2704-12 soybean

Outcome: Molecular characterization (which would indicate the information/data requirement for molecular characteristics)

2.3. Criteria for relevance

Criteria for establishing the relevance of retrieved publications were defined prior to conduct of the search. These criteria were modeled after those given in the EFSA 2019 explanatory note¹ and are described in [Table 1](#).

Table 1: Eligibility/inclusion criteria to establish the relevance of retrieved publications

Concepts	Criteria	Comment
Key elements of review questions with PECO structure		
Population	The publication addresses human and animal health, and/or the environment (including biodiversity, ecosystem services, service providing units, and endangered species) as general protection goals	From the publications that address the GMO under consideration, those that address protection goals relevant to the risk assessment of the GMO are eligible
Intervention/exposure	The publication addresses the GMO, derived food/feed products, and/or the intended trait(s) (e.g., newly expressed protein(s)) that are identical or like those under regulatory review	This enables the selection of publications that address the GMO, derived food/feed products, and/or the intended trait(s) under consideration
Comparator	If the publication reports a comparative study that uses plant material as test material, eligible publications must report a non-GM variety as comparator	In those cases where the publication addresses the GMO under consideration, reports a comparative analysis study and uses plant material as test material, eligible publications also need to include an appropriate non-GM line as comparator
Outcome	The publication addresses effects/impacts on human and animal health, and/or the environment	Publications that address the GMO under consideration also need to address effects/impacts on entities of concern, and potential determinants of exposure that place these entities at risk, in order to be relevant to the risk assessment of the GMO

Concepts	Criteria	Comment
Additional concepts		
Information/data requirements	The publication reports information pertaining to one or more information/data requirement(s) outlined in Appendix A for the GMO and derived food/feed products under consideration, including the intended trait(s)	Publications that potentially contribute to the knowledge informing the risk assessment of the GMO under consideration, and thus the risk hypotheses addressed, taking account of both hazard and exposure, can be considered relevant according to this eligibility/inclusion criterion. Publications addressing other issues such as benefits, socio-economics, ethics, crop protection, detection methods, efficacy, public perception and risk communication can be excluded, as they are not necessarily relevant to the risk assessment of GMOs
Plant species	The publication addresses the same plant species as the GMO under consideration	This eligibility/inclusion criterion permits the exclusion of publications on GMOs that contain the same intended trait(s) as the GMO under consideration, but which are introduced in another plant species
Scope of GMO application	The publication addresses pathways and levels of exposure to the GMO, derived food/feed products, and the intended trait(s) that are relevant for the intended uses of the GMO and derived food/feed products under regulatory review	From the publications that address the GMO under consideration, those that consider pathways and levels of exposure relevant to the scope of the GMO application (i.e., import and processing for food/feed uses, cultivation) are eligible
Target pests/organisms	The publication addresses target pests/organisms that are established in the EU	This permits the exclusion of publications that address interactions between the GMO and target pests/organisms that do not occur in the EU

Concepts	Criteria	Comment
Stacked events obtained by conventional crosses/subcombinations	The publication addresses the higher stacked event and/or a subcombination or subcombinations of the single events of the higher stacked event, independently of its/their origin	This permits the selection of publications on the higher stacked event and/or subcombinations of the single events of the higher stacked event that are in the scope of the GMO application(e), independently of their origin. This permits the exclusion of publications on the single events of the higher stacked event, because the risk assessment of GMO applications for stacked events covers only the products in the scope of the GMO application – i.e., the higher stacked event and subcombinations of the singles involved, independently of their origin
Molecular stacks	The publication addresses the molecular stack; all newly expressed proteins in the molecular stack; and/or one or several of the newly expressed proteins in the molecular stack that has/have not been previously risk assessed by EFSA and/or its GMO Panel and for which no safe use has been determined yet by EFSA and/or its GMO Panel	This permits the exclusion of publications that address one or several (not all) of the newly expressed proteins in the molecular stack that has/have been previously risk assessed by EFSA and/or its GMO Panel and for which the safe use has been determined by EFSA and/or its GMO Panel
Previously risk assessed publications	The publication has not been previously risk assessed by EFSA and/or its GMO Panel and is not cited/referenced in an EFSA/GMO Panel output	This permits the exclusion of publications that have been previously risk assessed by EFSA and/or its GMO Panel and cited/referenced in an EFSA/GMO Panel output
Access	Full-text document is accessible	If potentially relevant full-text documents cannot be obtained, they should be listed in a table with a description of the (unsuccessful) methods that have been used to try to obtain a copy

Concepts	Criteria	Comment
Reporting format	The publication presents original/primary data.	This permits the exclusion of publications that do not present original/primary data (e.g., editorials, position papers). Reviews should only be included if they present data that are not available from a primary research study
Reporting format	A study in a publication should only be presented once, but if it is presented in more than one publication, all publications should be listed and grouped	Duplicate publications should be excluded at the screening stage. Only one copy of a study is required even if it is reported in different publications, and identified in more than one database

Table adapted from EFSA, 2019: Explanatory note on literature searching conducted in the context of GMO applications for (renewed) market authorisation and annual post-market environmental monitoring reports on GMOs authorised in the EU market.

2.4. Reference publication

A publication previously identified for A2704-12 soybean was used to test and validate the search strategy:

- Federici S, Paraskevopoulos K (2018). Risk assessment of new sequencing information for genetically modified soybean A2704-12. EFSA Journal 16(11), e054696

3. SEARCH METHODS AND OUTCOMES

The search strategies used here followed the 2019 EFSA explanatory note on literature searching conducted in the context of GMO applications and post-market environmental monitoring activities¹. The search strategies were designed to be broad and sensitive enough to capture any relevant publications, if available.

An information specialist with background in plant biotechnology selected the databases, identified relevant search terms, developed search profiles, designed search strategies and conducted the searches.

3.1. Time window and date of the literature search

The database searches were performed on October 9, 2019. Only documents updated between October 1, 2018 and September 30, 2019, were considered in the search.

3.2. Search strategy

The search profiles were designed to cover event name, trade name, newly expressed proteins and intended traits. Since the 'trade name' profile, 'newly expressed protein' profile and 'intended trait' profile produced too many results when used on their own, they were combined with additional profiles: the 'trade name' profile and the 'newly expressed protein' profile were combined with a 'plant species' profile

while the 'intended trait' profile was combined with a 'general GMO' profile as well as with the 'plant species' profile. See [Table 2](#) for the detailed search profile.

All searches were performed in the Basic Index (BI) field, which includes the following subject headings/field names:

- **Agricola:** title (TI), controlled term (CT), supplementary term (ST), abstract (AB), named person (NA), corporate name (CO), note (NTE), geographic term, CABA and other fields (GT)
- **Biosis:** title (TI), abstract (AB), biosystematic codes (BC), chemical name (CN), controlled term (CT), gene name (GEN), geographic term (GT), organism (ORGN) and supplementary term (ST); as well as CAS Registry Numbers (RN)
- **CA-Plus:** title (TI), supplementary term (ST), index term (IT) and abstract (AB); as well as CAS Registry Numbers
- **CABA:** title (TI), controlled term (CT), supplementary term (ST), broader term (BT), abstract (AB), organism name (ORGN) and geographic term (GT); as well as CAS Registry Numbers
- **Medline:** title (TI), chemical name (CN), gene name (GEN), controlled term (excluding MeSH numbers) (CT), supplementary term (ST), named person (NA), other source (OS), and abstract (AB), as well as CAS Registry Numbers and GenBank Numbers

The search results were limited to documents updated between October 1, 2018 and September 30, 2019 (UP>=20181001 and UP<=20190930), and to non-patent documents (not P/DT). To ensure that documents with indexing errors where two DTs (one eligible and one ineligible) were attached to a single record were not missed, documents with both 'journal' and 'patent' as *document type* were also kept. These putative documents would be identified with (P/DT AND J/DT) in CABA and CAPlus.

See [Appendix 1](#) for a complete search history.

Table 2: Search profile for database search

Set	Search string	Concepts
1	LL27 or A2704-12 or A2704(w)12 or A(w)2704(w)12 or ACS-GM005-3 or ACS-GM005-3 or ACS-GM005-3 or ACS(w)GM005(w)3 or ACS(w)GM005(w)3 or ACS(w)GM005(w)3 or ACSGM005(w)3 or ACSGM005(w)3 or ACSGM005(w)3	Event name
2	libertylink or libertylinktm or libertylinkrtm or liberty(w)link or liberty(w)linktm or liberty(w)linkrtm or LL or LLTM or LLRTM	Trade name
3	((bar or pat) (2a) (gene# or protein# or enzyme#)) or ppt (2w) acetyltransferase or ppt (2w) acetyl (w) transferase or pt (w) n (2w) acetyltransferase or pt (w) n (2w) acetyl (w) transferase or phosphinothricin (w) n (w) acetyltransferase or phosphinothricin (2w) acetyltransferase or phosphinothricin (2w) acetyl (w) transferase or phosphinothricinacetyl (w) transferase	Newly expressed protein
4	(herbicide? or bialaphos or basta or glufosinate or phosphinothricin or liberty?) (5a) (resist? or toleran? or protect?)	Intended trait

5	soy or soya or soja or soybean# or soyabean# or sojabean# or glycine(w)max or g(w)max	Plant species
6	GMO OR GMOs OR LMO OR LMOs OR GM OR GE OR transgen? OR (genetic?(3a)(modif? OR transform? OR manipulatio? OR improv? OR engineer?))	GMO general
7	2 and 5	Trade name AND Plant species
8	3 and 5	Newly expressed protein AND Plant species
9	4 and 5 and 6	Intended trait AND Plant species AND GMO general
10	1 or 7 or 8 or 9	Event name OR (Trade name AND plant species) OR (Newly expressed protein AND Plant species) OR (Intended trait AND Plant species AND GMO general)

3.3. Databases used in the literature search

All searches were performed in the host STN (Scientific and Technical Information Network), an online database service operated jointly by CAS and FIZ Karlsruhe. STN provides access to a broad range of databases from the most renowned database producers worldwide.

The searches described here were performed in five databases: three multidisciplinary/large databases (Biosis, Medline and CA-Plus) and two subject-specific databases focused on agriculture-related topics (Agricola and CABA).

The dates of the most recent database updates are provided in [Table 3](#). See [Appendix 2](#) for detailed database descriptions.

Table 3: Overview of the selected databases and summary of search results from each database

Database	AGRICOLA	BIOSIS	CAB Abstracts	CAPLUS	MEDLINE
Database Provider	STN International	STN International	STN International	STN International	STN International
Coverage	1970-present	1926-present	1973-present	1907-present	1946-present
Date of search	11 Oct 2019	11 Oct 2019	11 Oct 2019	11 Oct 2019	11 Oct 2019
Datespan of the search	1 Oct 2018 – 30 Sept 2019	1 Oct 2018 – 30 Sept 2019	1 Oct 2018 – 30 Sept 2019	1 Oct 2018 – 30 Sept 2019	1 Oct 2018 – 30 Sept 2019
Latest database update	4 Oct 2019	9 Oct 2019	10 Oct 2019	10 Oct 2019	10 Oct 2019

Number of records after duplicate removal	16	29	20	27	31
Number of relevant records after rapid assessment	1	2	3	2	4

4. MANUAL SEARCHES

4.1. Manual searches of web pages of food safety, agriculture, and biotechnology-related authority webpages

A search of the web pages of regulatory authorities for food and feed safety, agriculture, and biotechnology was conducted. Search results were manually examined for relevant records that were either published during the time period of October 1, 2018 to September 30, 2019 or refer to relevant records published during this time frame. Relevance of results was determined based on the criteria listed in [Table 1](#) and are summarized in [Table 4](#). All web pages searched were chosen based on them being recommended as part of the EFSA 2019 explanatory note¹. Search terms consisted of LL27 OR A2704-12, LibertyLink soy 27 OR ACS-GMO05-3, PAT/pat OR Phosphinothricin in A2704-12 soybean. (All searched singly, with no search limits applied).

Table 4: Search of websites for regulatory authorities for food and feed safety, agriculture, and biotechnology

Source Site Name	Website URL	Date of Most Recent Site Update	Date of Search	No. of Relevant Records
US Environmental Protection Agency (EPA)	https://www.epa.gov/	Oct 4, 2019	Oct 8, 2019	0
US Department of Agriculture (USDA)	https://www.usda.gov/	Oct 8, 2019	Oct 9, 2019	0
US Food and Drug Administration (FDA)	https://www.fda.gov/	Oct 9, 2019	Oct 9, 2019	0
Health Canada	https://www.canada.ca/en/health-canada.html	Oct 7, 2019	Oct 9, 2019	0
Canadian Food Inspection Agency	https://www.canada.ca/en/food-inspection-agency.html	Aug 23, 2019	Oct 9, 2019	0
Environment and Climate Change Canada	https://www.canada.ca/en/services/environment/weather/climate-change.html	Jul 26, 2019	Oct 9, 2019	0

Source Site Name	Website URL	Date of Most Recent Site Update	Date of Search	No. of Relevant Records
Food Standards Australia New Zealand (FSANZ)	http://www.foodstandards.gov.au/Pages/default.aspx	Oct 9, 2019	Oct 9, 2019	0
Office of the Gene Technology Regulator (OGTR)	http://www.ogtr.gov.au/	Oct 8, 2019	Oct 9, 2019	0
National Technical Commission on Biosafety (CTNBio)	http://ctnbio.mcti.gov.br/en	September 2019	Oct 7-21, 2019	0
National Advisory Commission on Agricultural Biotechnology (CONABIA)	https://www.argentina.gob.ar/agroindustria/bioeconomia/biotechnologia	Oct 1, 2019	Oct 2, 2019	0
National Food Safety and Quality Service (SENASA)	https://www.argentina.gob.ar/senasa	Oct 2, 2019	Oct 2, 2019	0
Ministry of Environment, Forest, and Climate Change. Government of India	http://moef.gov.in/	Sept 30, 2019	Oct 9, 2019	0
Ministry of Agriculture, Forestry and Fisheries (MAFF)	http://www.maff.go.jp/	Oct 30, 2019	Oct 30, 2019	0
Ministry of Health, Labor and Welfare (MHLW)	http://www.mhlw.go.jp/	Oct 30, 2019	Oct 30, 2019	0

4.2. Manual searches of reference lists of recent review articles

Review articles published between October 1, 2018 and September 30, 2019 served as sources for reference lists to search for potentially relevant studies. The review articles were identified by searching of PubMed.gov for general terms such as “GMO” or “GM crops” in the titles and abstracts. A list of review articles and the resulting number of relevant studies found within the bibliographies is given in [Table 5](#).

Table 5: Documents for which reference lists were scanned for relevant studies

No	Author(s) and Year	Title	Source	Number of relevant bibliographic references retrieved
1	Agapito-Tenfen SZ, Okoli AS, Bernstein MJ, Wikmark OG, Myhr AI. 2018	Revisiting Risk Governance of GM Plants: The Need to Consider New and Emerging Gene-Editing Techniques.	Front Plant Sci. 2018 Dec 21;9:1874. doi: 10.3389/fpls.2018.01874.	0
2	Alarcon CM, Shan G, Layton DT, Bell TA, Whipkey S, Shillito RD. 2019	Application of DNA- and Protein-Based Detection Methods in Agricultural Biotechnology.	J Agric Food Chem. 2019 Jan 30;67(4):1019-1028. doi: 10.1021/acs.jafc.8b05157.	0
3	Bogner A, Torgersen H. 2018	Precaution, Responsible Innovation and Beyond - In Search of a Sustainable Agricultural Biotechnology Policy.	Front Plant Sci. 2018 Dec 18;9:1884. doi: 10.3389/fpls.2018.01884.	0
4	Boonchaisri S, Rochfort S, Stevenson T, Dias DA. 2019	Recent developments in metabolomics-based research in understanding transgenic grass metabolism.	Metabolomics. 2019 Mar 15;15(4):47. doi: 10.1007/s11306-019-1507-4.	0
5	Collins C, Lorenzen N, Collet B. 2019	DNA vaccination for finfish aquaculture.	Fish Shellfish Immunol. 2019 Feb;85:106-125. doi: 10.1016/j.fsi.2018.07.012.	0
6	Gaffar FY, Koch A. 2019	Catch Me If You Can! RNA Silencing-Based Improvement of Antiviral Plant Immunity.	Viruses. 2019 Jul 23;11(7). pii: E673. doi: 10.3390/v11070673.	0
7	Ghosh S, Ghosh S, Sil PC. 2019	Role of nanostructures in improvising oral medicine.	Toxicol Rep. 2019 Apr 15;6:358-368. doi: 10.1016/j.toxrep.2019.04.004.	0
8	Halford NG. 2019	Legislation governing genetically modified and genome-edited crops in Europe: the need for change.	J Sci Food Agric. 2019 Jan 15;99(1):8-12. doi: 10.1002/jsfa.9227.	0
9	Hamburger DJS. 2018	Normative Criteria and Their Inclusion in a Regulatory Framework for New Plant Varieties Derived From Genome Editing.	Front Bioeng Biotechnol. 2018 Dec 19;6:176. doi: 10.3389/fbioe.2018.00176.	0

No	Author(s) and Year	Title	Source	Number of relevant bibliographic references retrieved
10	Hundleby PAC, Harwood WA. 2019	Impacts of the EU GMO regulatory framework for plant genome editing.	Food Energy Secur. 2019 May;8(2):e00161. doi: 10.1002/fes3.161.	0
11	Ichim MC. 2019	The Romanian experience and perspective on the commercial cultivation of genetically modified crops in Europe.	Transgenic Res. 2019 Feb;28(1):1-7. doi: 10.1007/s11248-018-0095-9.	0
12	Ishaq N, Bilal M, Iqbal HMN. 2019	Medicinal Potentialities of Plant Defensins: A Review with Applied Perspectives.	Medicines (Basel). 2019 Feb 19;6(1). pii: E29. doi: 10.3390/medicines6010029.	0
13	Jyoti A, Kaushik S, Srivastava VK, Datta M, Kumar S, Yugandhar P, Kothari SL, Rai V, Jain A. 2019	The potential application of genome editing by using CRISPR/Cas9, and its engineered and ortholog variants for studying the transcription factors involved in the maintenance of phosphate homeostasis in model plants.	Semin Cell Dev Biol. 2019 Apr 6. pii: S1084-9521(18)30112-5. doi: 10.1016/j.semcdb.2019.03.010.	0
14	Kauffmann F, Van Damme P, Leroux-Roels G, Vandermeulen C, Berthels N, Beuneu C, Mali S. 2019	Clinical trials with GMO-containing vaccines in Europe: Status and regulatory framework.	Vaccine. 2019 Sep 30;37(42):6144-6153. doi: 10.1016/j.vaccine.2019.08.018.	0
15	Looi FY, Baker ML, Townson T, Richard M, Novak B, Doran TJ, Short KR. 2018	Creating Disease Resistant Chickens: A Viable Solution to Avian Influenza?	Viruses. 2018 Oct 15;10(10). pii: E561. doi: 10.3390/v10100561.	0
16	Mat Jalaluddin NS, Othman RY, Harikrishna JA. 2019	Global trends in research and commercialization of exogenous and endogenous RNAi technologies for crops.	Crit Rev Biotechnol. 2019 Feb;39(1):67-78. doi: 10.1080/07388551.2018.1496064.	0
17	Napier JA, Haslam RP, Tsalavouta M, Sayanova O. 2019	The challenges of delivering genetically modified crops with nutritional enhancement traits.	Nat Plants. 2019 Jun;5(6):563-567. doi: 10.1038/s41477-019-0430-z.	0

No	Author(s) and Year	Title	Source	Number of relevant bibliographic references retrieved
18	Rostoks N, Granti A, Levi A L, Levi A B, Evelone V, Valci A O, Aleksejeva I. 2019	Genetically modified seeds and plant propagating material in Europe: potential routes of entrance and current status.	Heliyon. 2019 Feb 15;5(2):e01242. doi: 10.1016/j.heliyon.2019.e01242.	0
19	Tyczewska A, Woźniak E, Gracz J, Kuczyński J, Twardowski T. 2018	Towards Food Security: Current State and Future Prospects of Agrobiotechnology.	Trends Biotechnol. 2018 Dec;36(12):1219-1229. doi: 10.1016/j.tibtech.2018.07.008.	0
20	Wolt JD, Wolf C. 2018	Policy and Governance Perspectives for Regulation of Genome Edited Crops in the United States.	Front Plant Sci. 2018 Nov 8;9:1606. doi: 10.3389/fpls.2018.01606.	0
21	Wu Y, Li J, Li X, Zhai S, Gao H, Li Y, Zhang X, Wu G. 2019	Development and strategy of reference materials for the DNA-based detection of genetically modified organisms.	Anal Bioanal Chem. 2019 Mar;411(9):1729-1744. doi: 10.1007/s00216-019-01576-w.	0
22	Zimny T, Sowa S, Tyczewska A, Twardowski T. 2019	Certain new plant breeding techniques and their marketability in the context of EU GMO legislation - recent developments.	N Biotechnol. 2019 Jul 25;51:49-56. doi: 10.1016/j.nbt.2019.02.003.	0

5. RESULTS OF THE STUDY IDENTIFICATION AND SELECTION PROCESS

The database searches ([Section 3](#)) identified a total of 177 references, which were reduced to 123 after removal of duplicates ([Table 3](#)). No additional studies were identified in the manual searches ([Section 4](#)).

5.1. Screening of titles and abstracts to exclude obviously irrelevant references (Stage 1)

All references identified in the database searches described in Section 3 were assessed for relevance based on the information in their title and abstract by two reviewers independently. If opinions of relevance differed, the discrepancies were discussed between the reviewers and if a disagreement persisted, the publication under the discussion was transferred to Stage 2 for detailed evaluation by the experts.

Clearly irrelevant records were tagged as “Not Relevant”. These included:

- Duplicate entries
- Secondary literature (reviews), other than assessments from regulatory authorities
- Articles on non-relevant topics like detection methods, socio-economic implications of GM crops, GM policy, agronomical performance, other herbicide resistant GM crops, unrelated topics, etc.

Publications which appeared to be relevant and those of unclear relevance were tagged as “Relevant” and progressed to Stage 2 (detailed assessment; see [Section 5.2](#)).

The number of publications excluded after rapid assessment for relevance is presented in [Table 6](#).

5.2. Detailed assessment of eligible references (Stage 2)

Publications tagged as “Relevant” in Stage 1 were assessed in detail independently by two scientific experts in each of three corresponding areas (i.e., Molecular Characterization, Food and Feed Safety, Environmental Safety), based on the full text of the publications.

If opinions of relevance differed between reviewers within each area, the initial reviewers discussed the discrepancy as necessary and consulted additional reviewers to resolve the discrepancy if needed. All eligible references were assessed in detail. This detailed assessment included evaluation of the scope of the article as well as the quality and reliability of the study. Categorization of reliability (as described in the EFSA 2019 explanatory note¹ and reported in [Table 11](#)) was dependent upon the following:

- appropriateness of methodology
- whether the description of methodology would allow independent repetition of the study
- extent of characterization of test materials
- reporting of evidence of reproducibility

[Table 6](#) gives an overview of the reference selection process and results of the detailed assessment.

Table 6: Results of the publication selection process

Total number of publications retrieved after all searches of the scientific literature (excluding duplicates)	123
Number of publications excluded from the search results after rapid assessment for relevance (Stage 1)	111
Total number of full-text documents assessed in detail	12
Number of publications excluded from further consideration after detailed assessment for relevance (Stage 2)	12
Total number of unobtainable/unclear publications	0
Total number of relevant publications	0

[Table 7](#) lists the publications determined to be relevant along with their potential impact on the safety assessment after detailed evaluation. Publications that were clearly not relevant after a detailed assessment are listed in [Table 8](#). [Table 9](#) lists the publications for which full-text documents were unobtainable for detailed assessment or for which relevance was unclear after detailed assessment.

Table 7: Report of all relevant publications retrieved after detailed assessment of full-text documents for relevance: ordered by category of information/data requirement(s)

Main category of information/data requirement	Study (Author(s) and year)	Title	Source
No publications in this category.			

Table 8: Report of publications excluded from the risk assessment after detailed assessment of full-text documents

Study (Author(s) and year)	Title	Source	Reason(s) for exclusion based on eligibility/inclusion criteria listed in Table 1
Federici, S. Paraskevopoulos, K. 2018	Risk assessment of new sequencing information for genetically modified soybean A2704-12 .	EFSA Journal (2018), Volume 16, Number 11, e05496 p., 4 refs. ISSN: 1831-4732 DOI: 10.2903/j.efsa.2018.5496 Published by: Wiley, Oxford	This publication was excluded because it does not contain primary/original data.
Zou Shiyong Qi Xiaozhe Lu Jiao Luo Yunbo Huang Kunlun Delaney Bryan Xu Wentao He Xiaoyun 2018	The food safety of DP-356O43 soybeans on SD rats reflected by physiological variables and fecal microbiota during a 90-day feeding study.	Regulatory toxicology and pharmacology : RTP, (2018 Aug) Vol. 97, pp. 144-151.	The study did not examine A2704-12 soybean.

Study (Author(s) and year)	Title	Source	Reason(s) for exclusion based on eligibility/inclusion criteria listed in Table 1
Herman Rod A Ekmay Ricardo D Schafer Barry W Song Ping Fast Brandon J Papineni Sabitha Shan Guomin Juberg Daland R 2018	Food and feed safety of DAS-44406-6 herbicide - tolerant soybean.	Regulatory toxicology and pharmacology : RTP, (2018 Apr) Vol. 94, pp. 70-74.	The study did not examine A2704-12 soybean.
Qian Zhi-Yong Zhang Shu-Jing Zhang Li Zhang Jing Liu Ying-Hua Zhou Qing-Hong Jiang Shu-Qing Li Shu-Fei 2018	Subchronic toxicity study in rats evaluating genetically modified DAS-81419-2 soybean .	Regulatory toxicology and pharmacology : RTP, (2018 Jul) Vol. 96, pp. 48-56.	The study evaluates the safety of the expressed proteins Cry1Ac, Cry1F and PAT in soybean - a molecular stack that has been previously evaluated by EFSA and/or its GMO Panel for which safe use has been determined by EFSA and/or its GMO Panel. The study did not examine A2704-12 soybean.
Papineni Sabitha Passage Julie K Thomas Johnson Ekmay Ricardo D 2018	Evaluation of 30% DAS-44406-6 soybean meal in a subchronic rat toxicity study.	Regulatory toxicology and pharmacology : RTP, (2018 Apr) Vol. 94, pp. 57-69.	The study did not examine A2704-12 soybean.
Papineni, Sabitha Fletcher, Dale W. Cromwell, Gary L. Ekmay, Ricardo D. 2017	Comparative performance of broilers fed diets containing DAS-44406-6 and non-transgenic soybean meal.	Poultry Science, (MAY 2017) Vol. 96, No. 5, pp. 1244-1249.	The study did not examine A2704-12 soybean.

Study (Author(s) and year)	Title	Source	Reason(s) for exclusion based on eligibility/inclusion criteria listed in Table 1
Then, Christoph and Bauer-Panskus, Andreas 2017	Possible health impacts of Bt toxins and residues from spraying with complementary herbicides in genetically engineered soybeans and risk assessment as performed by the European Food Safety Authority EFSA.	Environmental Sciences Europe, (JAN 11 2017) Vol. 29, pp. Article No.: 1.	The study did not examine A2704-12 soybean.
Papineni, Sabitha Christina M Dunville Ekmay Ricardo Jennifer A Murray Johnson Thomas Radha Krishna Sura 2017	Evaluation of the safety of a genetically modified DAS-44406-6 soybean meal and hulls in a 90-day dietary toxicity study in rats	Food and chemical toxicology (2017), pp. 245-252.	The study did not examine A2704-12 soybean.

Study (Author(s) and year)	Title	Source	Reason(s) for exclusion based on eligibility/inclusion criteria listed in Table 1
Naegeli, H. Bresson, J. L. Dalmay, T. Dewhurst, I. C. Epstein, M. M. Firbank, L. G. Guerche, P. Hejatko, J. Moreno, F. J. Mullins, E. Nogue, F. Rostoks, N. Serrano, J. J. S. Savoini, G. Veromann, E. Veronesi, F. Alvarez, F. Ardizzzone, M. Papadopolou, N. Paraskevopoulos, K. 2019	Assessment of genetically modified soybean A2704 -12 for renewal of authorisation under regulation (EC) No 1829/2003 (application EFSA-GMO -RX-009).	EFSA Journal (2019), Volume 17, Number 1, e05523 p.,	This publication was excluded because it does not contain original/primary data.

Study (Author(s) and year)	Title	Source	Reason(s) for exclusion based on eligibility/inclusion criteria listed in Table 1
Naegeli, H. Bresson, J. L. Dalmay, T. Dewhurst, I. C. Epstein, M. M. Firbank, L. G. Guerche, P. Hejatko, J. Moreno, F. J. Mullins, E. Nogue, F. Rostoks, N. Juan, J. Serrano, S. Savoini, G. Veromann, E. Veronesi, F. Alvarez, F. Ardizzzone, M. Paraskevopoulos, K. 2018	Assessment of genetically modified soybean MON 89788 for renewal of authorisation under Regulation (EC) No 1829/2003 (application EFSA-GMO -RX-011).	EFSA Journal (2018), Volume 16, Number 11, e05468 p., 6 refs. ISSN: 1831-4732 DOI: 10.2903/j.efsa.2018.5468 Published by: Wiley, Oxford	A2704-12 soybean was not the subject of this document.

Study (Author(s) and year)	Title	Source	Reason(s) for exclusion based on eligibility/inclusion criteria listed in Table 1
EFSA Panel on Genetically Modified Organisms Naegeli, Hanspeter Birch, Andrew Nicholas Casacuberta, Josep De Schrijver, Adinda Gralak, Mikolaj Antoni Jones, Huw Manachini, Barbara Messean, Antoine Nielsen, Elsa Ebbesen Nogue, Fabien Robaglia, Christophe Rostoks, Nils Sweet, Jeremy Tebbe, Christoph Visioli, Francesco Wal, Jean-Michel Ardizzzone, Michele Devos, Yann Gomes, Ana Liu, Yi Neri, Franco Maria Olaru, Irina 2017	Scientific Opinion on an application by Dow AgroSciences LLC (EFSA-GMO -NL-2011-91) for the placing on the market of genetically modified herbicide -tolerant soybean DAS-68416-4 for food and feed uses, import and processing under Regulation (EC) No 1829/2003.	EFSA Journal (2017), 15(3), n/a CODEN: EJFOA6; ISSN: 1831-4732	A2704-12 soybean was not the subject of this document.

Study (Author(s) and year)	Title	Source	Reason(s) for exclusion based on eligibility/inclusion criteria listed in Table 1
EFSA Panel on Genetically Modified Organisms Naegeli, Hanspeter Birch, Andrew Nicholas Casacuberta, Josep De Schrijver, Adinda Gralak, Mikolaj Antoni Jones, Huw Manachini, Barbara Messean, Antoine Nielsen, Elsa Ebbesen Nogue, Fabien Robaglia, Christophe Rostoks, Nils Sweet, Jeremy Tebbe, Christoph Visioli, Francesco Wal, Jean-Michel Alvarez, Fernando Ardizzone, Michele Liu, Yi Neri, Franco Maria Ramon, Matthew 2017	Scientific opinion on an application by Dow AgroSciences LLC (EFSA-GMO -NL-2012-106) for the placing on the market of genetically modified herbicide -tolerant soybean DAS-44406-6 for food and feed uses, import and processing under Regulation (EC) No 1829/2003	EFSA Journal (2017), 15(3), n/a CODEN: EJFOA6; ISSN: 1831-4732	A2704-12 soybean was not the subject of this document.

Table 9: Report of unobtainable/unclear publications

Study (Author(s) and year)	Title	Source	Description of (unsuccessful) methods used to try and obtain a copy of the publication
No publications in this category.			

6. NARRATIVE SYNTHESIS AND SUMMARY OF RELEVANT STUDIES

A total of 12 publications were selected during Stage 1 evaluation (rapid assessment based on title and abstract). After Stage 2 evaluation (detailed review based on full text), it was determined that none of the 12 publications were relevant for the safety assessment of the A2704-12 soybean and the newly expressed PAT/*pat* protein.

[Table 10](#) and [Table 11](#) list the relevant publications along with a summary of any adverse effects reported and the reliability of the publications.

Table 10: Summary of all relevant publications retrieved after detailed assessment of full-text documents for relevance(Stage 2): ordered by category of information/data requirement(s)

Main category of information/data requirement	Study (Author(s) and year)	Intervention/ test materials used	Adverse effects reported	Which adverse effect reported
No publications in this category.				

Table 11: Report of the reliability and implications for the risk assessment of all relevant publications retrieved after detailed assessment of full-text documents for relevance(Stage 2): ordered by category of information/data requirement(s)

Main category of information/data requirement	Study (Author(s) and year)	Summary of reliability appraisal	Implications for risk assessment
No publications in this category.			

7. CONCLUSION

The literature searches performed for A2704-12 soybean and the PAT/*pat* for the period from October 1, 2018 to September 30, 2019, identified a total of 123 unique publications. A total of 12 publications were progressed for detailed assessment after excluding 111 obviously irrelevant publications during Stage 1 evaluation (rapid assessment based on title and abstract).

These 12 publications were evaluated in detail based on their full text for potential relevance, following the pre-established criteria. No relevant references with bearing on human and animal safety, molecular characterization or environmental safety were identified. No issues or topics were identified that would trigger or warrant a more specific question formulation.

8. REFERENCES

No.	Author(s), title, source, edition, year, pages
1.	Devos Y, Guajardo IM, Alvarez F and Glanville J. Explanatory note on literature searching conducted in the context of GMO applications for (renewed) market authorisation and annual post-market environmental monitoring reports on GMOs authorised in the EU market. EFSA supporting publications 2019:EN-1614. 62 pages. doi:10.2903/sp.efsa.2019.EN-1614.

9. APPENDICES

Appendix 1 Search history

```
FILE 'MEDLINE, BIOSIS, AGRICOLA, CABA, HCAPLUS' ENTERED AT 09:20:39 ON 11
OCT 2019
L1      114 SEA LL27 OR A2704-12 OR A2704(W) 12 OR A(W) 2704(W) 12 OR
        ACS-GM005-3 OR ACS-GM005-3 OR ACS-GMO05-3 OR ACS(W) GM005(W) 3
        OR ACS(W) GM005(W) 3 OR ACS(W) GMO05(W) 3 OR ACSGM005(W) 3 OR
        ACSGM005(W) 3 OR ACSGMO05(W) 3
L2      50387 SEA LIBERTYLINK OR LIBERTYLINKTM OR LIBERTYLINKRTM OR LIBERTY(W
        ) LINK OR LIBERTY(W) LINKTM OR LIBERTY(W) LINKRTM OR LL OR
        LLTM OR LLRTM
L3      12373 SEA ((BAR OR PAT)(2A)(GENE# OR PROTEIN# OR ENZYME#)) OR
        PPT(2W) ACETYLTRANSFERASE OR PPT(2W) ACETYL(W) TRANSFERASE OR
        PT(W) N(2W) ACETYLTRANSFERASE OR PT(W) N(2W) ACETYL(W)
        TRANSFERASE
L4      1861 SEA PHOSPHINOTHRICIN(W) N(W) ACETYLTRANSFERASE OR PHOSPHINOTHRI
        CIN(2W) ACETYLTRANSFERASE OR PHOSPHINOTHRICIN(2W) ACETYL(W)
        TRANSFERASE OR PHOSPHINOTHRICINACETYL(W) TRANSFERASE
L5      12994 SEA (L3 OR L4)
L6      60746 SEA (HERBICID? OR BIALAPHOS OR BASTA OR GLUFOSINATE OR
        PHOSPHINOTHRICIN OR LIBERTY?) (5A) (RESIST? OR TOLERAN? OR
        PROTECT?)
L7      846740 SEA SOY OR SOYA OR SOJA OR SOYBEAN# OR SOYABEAN# OR SOJABEAN#
        OR GLYCINE(W) MAX OR G(W) MAX
L8      4759288 SEA GMO OR GMOS OR LMO OR LMOS OR GM OR GE OR TRANSGEN? OR
        (GENETIC?(3A) (MODIF? OR TRANSFORM? OR MANIPULAT? OR IMPROV? OR
        ENGINEER?))
L9      517 SEA L2 AND L7
L10     759 SEA L5 AND L7
L11     6850 SEA L6 AND L7 AND L8
L12     7900 SEA L1 OR L9 OR L10 OR L11
L13     2845 SEA L12 NOT P/DT
L14     0 SEA L12 AND (P/DT AND J/DT)
L15     2845 SEA L13 OR L14
L16     333 SEA L15 AND PY>=2017
L17     177 SEA L16 AND UP>=20181001 AND UP<=20190930
L18     123 DUP REM L17 (54 DUPLICATES REMOVED)
        ANSWERS '1-31' FROM FILE MEDLINE
        ANSWERS '32-60' FROM FILE BIOSIS
        ANSWERS '61-76' FROM FILE AGRICOLA
        ANSWERS '77-96' FROM FILE CABA
        ANSWERS '97-123' FROM FILE HCAPLUS
```

Appendix 2 Database descriptions

Host	File	Description
STN	AGRICOLA	<p>Agriculture Online Access is a bibliographic database containing selected worldwide literature of agriculture and related fields. AGRICOLA is the locator and bibliographic access and control system of the National Agricultural Library (NAL) collections and also includes records from other cooperating institutions. Coverage of the database includes agricultural economics and rural sociology, agricultural production, animal sciences, chemistry, entomology, food and human nutrition, forestry, natural resources, pesticides, plant science, soils and fertilizers, and water resources. Also covered are related areas such as biology and biotechnology, botany, ecology, and natural history.</p> <p>The database draws on bibliographies, serial articles, book chapters, monographs, computer files, serials, maps, audiovisuals, and reports. Bibliographic information, abstracts, geographic terms, controlled terms, and supplementary terms are searchable.</p>
STN	BIOSIS	<p>BIOSIS Previews® is the largest and most comprehensive life science database in the world. Amongst others subject coverage includes Agriculture, Biochemistry, Biophysics, Botany, Environmental Biology, Physiology, Toxicology.</p> <p>Sources include periodicals, journals, conference proceedings, reviews, reports, patents, and short communications. Nearly 6,000 life source journals, 1,500 international meetings as well as review articles, books, and monographs are reviewed for inclusion.</p> <p>Bibliographic information, indexing terms, abstracts, and CAS Registry Numbers are all searchable.</p>
STN	CABA/CAB	<p>The CAB Abstracts database covers worldwide literature from all areas of agriculture and related sciences including Agriculture, Agricultural chemicals, Animal sciences and production, Crop protection, Crop sciences and production, Environment, Soils and fertilizers.</p> <p>Sources for CABA include journals, books, reports, published theses, conference proceedings, and patents.</p> <p>Bibliographic information, indexing terms, abstracts, and CAS Registry Numbers are searchable.</p>
STN	CAS-CA/CAPLUS	<p>The Chemical Abstracts (CA) database covers all areas of Biochemistry, Chemistry and Chemical engineering, and related sciences.</p> <p>Sources include over 8,000 journals, patents from 38 national patent offices and two international patent organizations, technical reports, books, conference proceedings, and dissertations. Electronic only journals and Web preprints are also covered.</p> <p>Bibliographic terms, indexing terms, roles, CAS Registry Numbers, International Patent Classification, and abstracts are searchable.</p>

Host	File	Description
STN	MEDLINE	<p>MEDLINE contains information on every area of medicine. The MEDLINE database corresponds to Index Medicus, Index to Dental Literature, and International Nursing Index; OLDMEDLINE, with data from NLM's from the Cumulated Index Medicus (1960-1965) and Current List of Medical Literature (1958-1959); and, since August 2001, IN-PROCESS records, the latest documents before they have been completely indexed for inclusion on MEDLINE.</p> <p>Sources include journals and chapters in books or symposia. Bibliographic information, indexing terms, abstracts, chemical names, and CAS Registry Numbers are all searchable.</p> <p>Online thesauri are available for the Medical Subject Headings (/MN), Controlled Terms (/CT) and Chemical Name (/CN) fields.</p>