International protocols and conventions of biosafety, regulatory frameworks in different countries, field trials, identification of GMO in food…

Biosafety Concerns and Regulatory Framework (Chawla, 2009, Plant biotechnology)

Regulations and biosafety, Field testing of transgenic plants (Stewart, 2016, Plant biotechnology and genetics)

1

INTERNATIONAL PROTOCOLS AND CONVENTIONS ON BIOSAFETY

There have been various conventions, protocols and treaties for safe use of GMOs and their products. A **Convention on Biological Diversity (CBD)** was adopted in June 1992 which came into force in 1993.

Under this convention contracting parties agreed to consider and develop appropriate procedures to address the safe transfer, handling and use of any living modified organisms (LMOs).

CBD recognized that biotechnology inventions may have adverse effects on conservation and sustainable use of biological diversity (Article 19.3 of CBD) and a biosafety protocol, named as **Cartagena protocol,** is the result of that process. It incorporates the use of **precautionary principle**.

The aim of Cartagena protocol: ensuring an adequate level of protection in transfer, handling and use of genetically improved organisms, particularly during their trans-boundary movement.

The Biosafety Clearing-House (BCH) is a mechanism set up by the Cartagena Protocol on Biosafety to facilitate the exchange of information on Living Modified Organisms (LMOs) and assist the Parties to better comply with their obligations under the Protocol.

https://bch.cbd.int/

2

European Union:
The deliberate release of GMOs into the environment is under the **Directive 2001/18/EC.** The Directive puts in place a step by step approval process on a case by case assessment of the risks to human health and the environment before any GMO or product consisting of, or containing GMOs can be released to the environment or placed on the market.

EU regulatory framework: Deliberate Release of GMOs

DIRECTIVE 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. (OJ L 106, 17.4.2001, p. 1)

GMOs destined for food or feed, and medicinal GMOs for human or veterinary use are subject to specific legal provisions, defined in Regulation (EC) No 1829/2003 and Regulation (EC) No 726/2004 respectively.

REGULATION (EC) No 1830/2003 of the European Parliament and of the Council of 22 September 2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms and amending Directive 2001/18/EC. (OJ L 268, 18.10.2003, p. 24)

https://www.biosafety.be/content/eu-regulatory-framework-deliberate-release-gmos

3

Biosafety worldwide - Historical background
(Vir: https://www.biosafety.be/content/biosafety-worldwide-historical-background-3)

In 1982, the OECD published a first report dedicated to biotechnology (Bull, Holt and Lilly. Biotechnology: International trends and perspectives, ISBN 92-64-22362-2). It was the first intergovernmental document on the topic that took into account the environmental safety of GMOs and placed emphasis on the necessity of developing safety measures relating to new biotechnologies. Following recommendations from this report, in 1986 the OECD published a new report entitled: "Recombinant DNA Safety Considerations", later known as the "Blue Book".

https://www.biosafety.be/sites/default/files/m00032689.pdf

Stewart N. 2016. Plant biotechnology and genetics. Principles, techniques and applications.
HISTORY OF GENETIC ENGINEERING AND ITS REGULATION

4

Some web resources

OECD BioTrack Product Database - OECD public database allows regulatory officials and other interested stakeholders to easily share basic information on products derived from the use of modern biotechnology, as well as some products with novel traits acquired by the use of conventional breeding or mutagenesis, that have been approved for commercial application in at least one country, in terms of food, feed or environmental safety.
https://biotrackproductdatabase.oecd.org/

European Food Safety Authority (EFSA) – The European Food Safety Authority is the agency of the European Union that provides independent scientific advice and communicates on existing and emerging risks associated with the food chain
www.efsa.europa.eu

International Service for the Acquisition of Agri-biotech Applications (ISAAA), publishes Global Status of Commercialized Biotech Crops annually.
http://www.isaaa.org/gmapprovaldatabase/default.asp

GMO register
https://food.ec.europa.eu/plants/genetically-modified-organisms/gmo-register_en

European Comission website about GMO, legislation, approved GMOs (GMO register)
https://food.ec.europa.eu/plants/genetically-modified-organisms_en

5

Field trials with GMO in EU

Notifications per year/country (including plants and other than plants)

Year

Country	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Grand Total
Austria						2	1																							3
Belgium		26	16	17	11	7	7	6	8	16	5	8	1	2			1	3	1	2	1	5	1	2	2	1	3	6	1	159
Czech Republic															2	6	3	3	4	4	4	2		1	1	2	2	1	1	36
Denmark		5	1	5	4	5	10	4	5	1					1	2	5	2	4		2	1								57
Estonia																						1								1
Finland					1	3	6	3	3	3	1			1	1			2	2				1		1			1		29
France			36	57	69	91	72	70	64	34	17	3	17	11	14	32	2		2	1		6	8		7	2			1	616
Germany		3	1	8	12	17	20	18	23	7	8	7	9	10	7	11	12	7	8	3	10	6	6		7	14	4	27	24	289
Greece						1	5	7	6																					19
Hungary															10	9	7	3	1	2	1	5	1	1	1	1	6	4	2	54
Iceland														1					1			1								3
Ireland							2	2				1				1				1	2	1	2	2				1		15
Italy			5	19	43	50	46	43	51	18	5	9	2	4					1	1						2	3		1	303
Lithuania																1	1													2
Netherlands	4	15	9	25	16	10	14	19	5		19	4	4	7	7	9	5	8	4	5	4	6	5	4	12	11	6	12	28	277
Norway									1																					1
Poland														1	2	3	1	3	2	2	2	1	1	1						19
Portugal			2	2	1		3	3	1						4	5	2	2	1	1						2			1	30
Romania																	14	9	21	8	5		1				2		1	61
Slovakia																1		4	3	4	2	1	1							16
Slovenia																			1					1					1	3
Spain			3	10	11	16	44	39	39	19	19	17	40	20	26	51	36	50	65	49	28	40	21	10	15	11	11	36	28	754
Sweden					8	10	9	8	19	6	2	2	1	14	4	6	5	6	5	6	8	4	2	5	4	5	5	2	3	149
United Kingdom		16	17	23	37	27	25	22	13	25	12	5	8	1		2	1	3	1	3	3	4	2	1	1	5	2	2	6	267
Grand Total	4	65	90	166	213	239	264	244	238	129	88	56	82	72	78	139	95	105	127	92	72	84	52	28	51	56	44	92	98	###

https://gmoinfo.jrc.ec.europa.eu/overview-main.aspx

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European Union Reference Laboratory for GM Food and Feed (EU-RL GMFF)
http://gmo-crl.jrc.ec.europa.eu/

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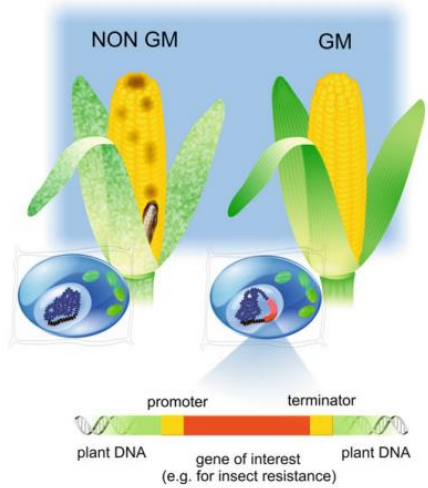

Fig. 1 Comparison of GM insect resistant and non-GM maize. The recombinant DNA sequence present in GM maize, target for the DNA-based detection of GM, is enlarged

https://link.springer.com/content/pdf/10.1007%2F978-1-4614-1390-5.pdf

8

In the European Union, laboratories can be designated by competent authorities to carry out the analysis of samples taken during official controls only if they operate, are assessed, and accredited in accordance with the EN ISO/IEC 17025 standards

The EN ISO/IEC 17025 standard has two main parts: one on management requirements and another on technical requirements.

Fig. 3 Scheme showing unidirectional route of sample in GMO testing from the first contact with the customer, through analyses in the laboratory, and issue of the final test report to the customer. Wherever possible, separate rooms (or chambers) should be assured for performing each stage of the procedure

Another important factor to consider in the organization of a GMO testing laboratory is the temperature. Room temperature control (e.g., 23 ± 3 °C) guarantees that pipetting of small volumes is not influenced by the environment.

Žel, J., Milavec, M., Morisset, D., Plan, D., Van den Eede, G., & Gruden, K. (2011). *How to Reliably Test for GMOs*: Springer US.

9

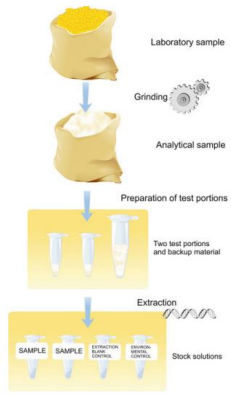

Fig. 12 Work flow of the sample showing the process from homogenization of the laboratory sample, preparation of test portions, extraction of DNA, and finally acquisition of stock solutions of DNA for further analysis

The laboratory sample should be of a size that ensures the quantification of GMO with a statistical degree of confidence of 95%. Given the threshold value of 1% of GM material within conventional material (in the case of expected inhomogeneous distribution of GMO particles in the investigated material) and taking into account an overall sampling error of 20%, laboratory samples for GMO analysis should contain at least 10,000 particles (Hubner et al. 2001)

Žel, J., Milavec, M., Morisset, D., Plan, D., Van den Eede, G., & Gruden, K. (2011). *How to Reliably Test for GMOs*: Springer US.

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Detection Procedure Using DNA-Based Methods

1) *Screening test* (P-35S, T-NOS and other frequently used elements). An example of multiplex method to identify at the same time 5 elements (Waiblinger et al. 2010): P-35S, T-NOS, CTP2-CP4EPSPS, P-35S-pat, bar.
2) If the screening test is positive, identification of GMOs is performed with event-specific methods.

Fig. 8 Screening methods target a part of rDNA sequence that is present in many GMOs, such as the regulatory sequences of promoters, terminators, or construct-specific sequences

Žel, J., Milavec, M., Morisset, D., Plan, D., Van den Eede, G., & Gruden, K. (2011). *How to Reliably Test for GMOs*: Springer US.

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Fig. 9 Event-specific methods allowing unique identification of the individual GMO present in the sample, usually targeting the nucleotide sequence at the junction between the plant host genome and the rDNA

Quantification of GMOs in the sample

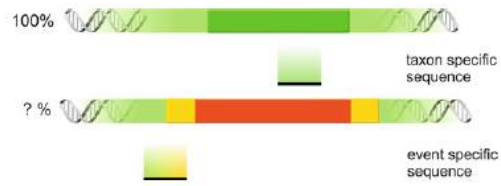

Fig. 10 Quantification of GMO is done by measuring the ratio between taxon-specific sequence and event-specific sequence

Žel, J., Milavec, M., Morisset, D., Plan, D., Van den Eede, G., & Gruden, K. (2011). *How to Reliably Test for GMOs*: Springer US.

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The growth in patents related to agricultural biotechnology

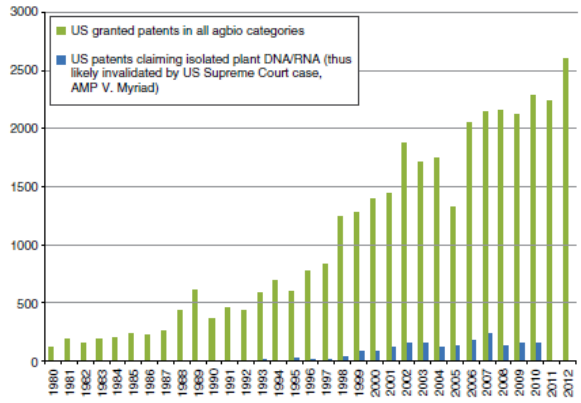

Figure 15.1. Annual trends in plant biotechnology based on patents granted by the US Patent and Trademark office between 1980 and 2012. Analysis includes US patents granted and corresponding to the international patent class categories considered relevant in agricultural biotechnology (gray bars, Data Source: Thomson Innovation 2013; http://info.thomsoninnovation.com). Included are US patents claiming isolated DNA/RNA sequences that are likely to become invalidated by the US Supreme Court. (*Source*: Adapted from Graff et al. (2013).)

Stewart, C. N. (2016). *Plant Biotechnology and Genetics: Principles, Techniques, and Applications*: Wiley.

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US008273954B1

(12) **United States Patent**
Rogers et al.

(10) **Patent No.: US 8,273,954 B1**
(45) **Date of Patent: Sep. 25, 2012**

(54) **GENETICALLY TRANSFORMED PLANTS**

(75) Inventors: **Stephen G. Rogers**, MO (US); **Robert B** MO (US); **Robert T** MO (US)

(73) Assignee: **Monsanto Technolo** MO (US)

(*) Notice: Subject to any discla patent is extended U.S.C. 154(b) by 0 d

(21) Appl. No.: **06/793,486**

(22) Filed: **Oct. 30, 1985**

Related U.S. Applicatio

(63) Continuation of application No. Jan. 17, 1983, now abandoned.

(51) **Int. Cl.**
C12N 15/84 (2006.01)
C12N 15/54 (2006.01)

(52) **U.S. Cl.** **800/2**

(58) **Field of Classification Search**

See application file for complete search history.

Zambryski et al, J. Mol. Appl. Genet. vol. 1 No. 8 pp. 361-370

(57) **ABSTRACT**

This invention relates to genetically transformed, non-tumorous plant cells. A modified Ti plasmid is created which contains a left T-DNA border, one or more desired genes, and a right T-DNA border. This region does not contain tumorigenic or phytohormone-altering genes. The Ti plasmid is inserted into plant cells, where the T-DNA region is transferred into the plant genome. The transformed plant cells may be regenerated into morphologically normal plants which will pass the desired gene(s) to their descendants.

24 Claims, 37 Drawing Sheets

Keith et al. EMBO Journal 5(10): 2419-2425 (1986).*

US 8,273,954 (Rogers et al. 2012) patent covering a broad Agrobacterium-mediated transformation method for dicotyledonous plants, which is owned by Monsanto and has an anticipated expiration date in 2029 (Stewart, N. 2016).

https://patents.google.com/patent/US8273954B1/en

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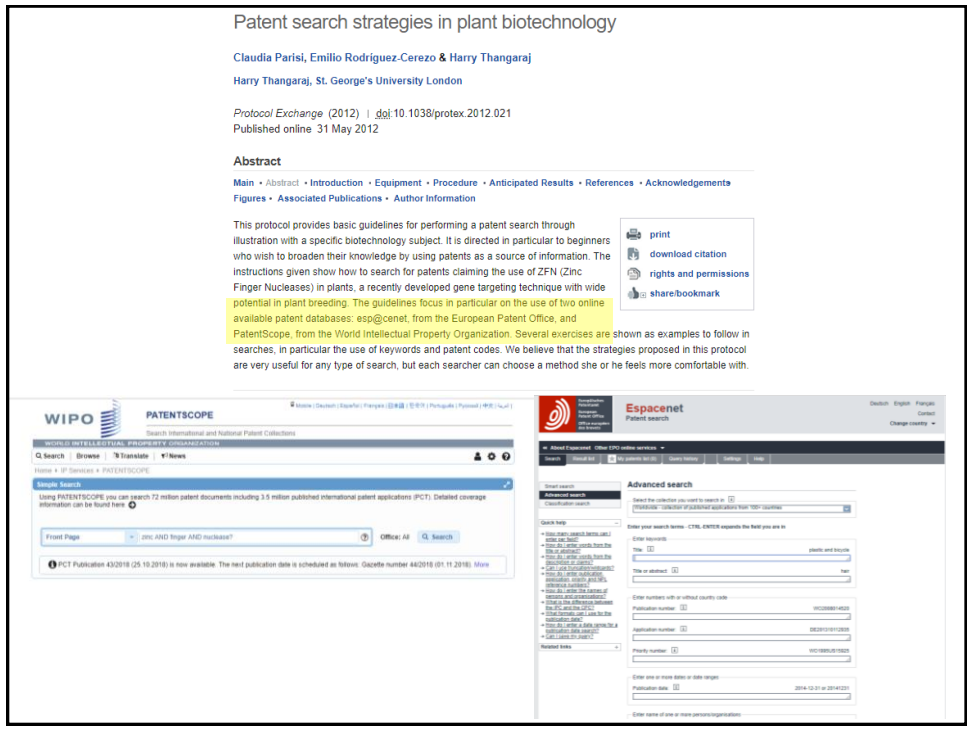
Patent search strategies in plant biotechnology
Claudia Parisi, Emilio Rodriguez-Cerezo & Harry Thangaraj
Harry Thangaraj, St. George's University London
Protocol Exchange (2012) | doi:10.1038/protex.2012.021
Published online 31 May 2012
Abstract
Main • Abstract • Introduction • Equipment • Procedure • Anticipated Results • References • Acknowledgements
Figures • Associated Publications • Author Information
This protocol provides basic guidelines for performing a patent search through illustration with a specific biotechnology subject. It is directed in particular to beginners who wish to broaden their knowledge by using patents as a source of information. The instructions given show how to search for patents claiming the use of ZFN (Zinc Finger Nucleases) in plants, a recently developed gene targeting technique with wide potential in plant breeding. The guidelines focus in particular on the use of two online available patent databases: esp@cenet, from the European Patent Office, and PatentScope, from the World Intellectual Property Organization. Several exercises are shown as examples to follow in searches, in particular the use of keywords and patent codes. We believe that the strategies proposed in this protocol are very useful for any type of search, but each searcher can choose a method she or he feels more comfortable with.
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