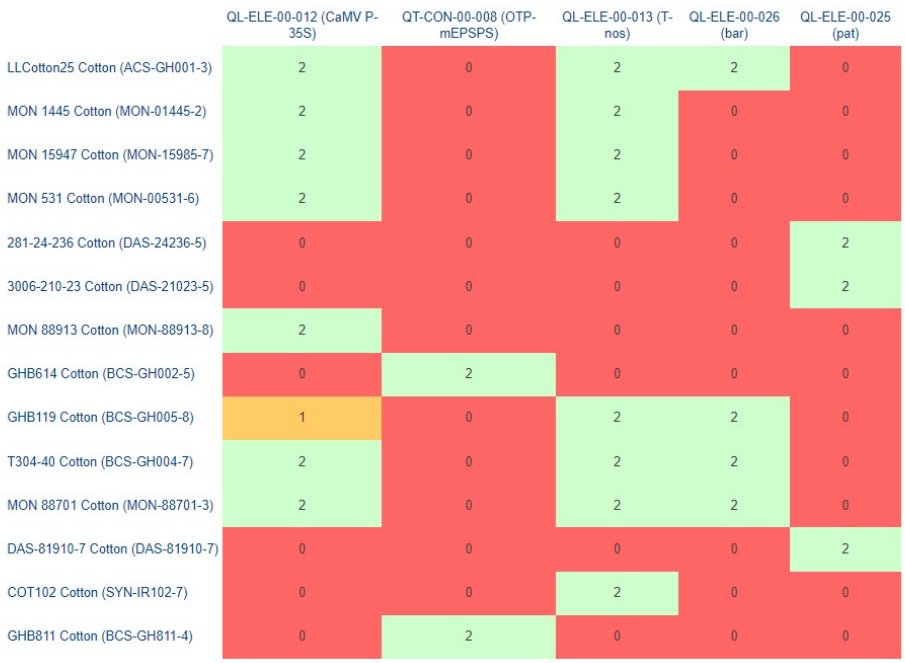
European Commission

JRC TECHNICAL REPORT

In Silico Proposal of Screening Strategies for Detecting EU Authorised GMOs



	QL-ELE-00-012 (CaMV P-35S)	QT-CON-00-008 (OTP-mEPSPS)	QL-ELE-00-013 (T-nos)	QL-ELE-00-026 (bar)	QL-ELE-00-025 (pat)
LLCotton25 Cotton (ACS-GH001-3)	2	0	2	2	0
MON 1445 Cotton (MON-01445-2)	2	0	2	0	0
MON 15947 Cotton (MON-15985-7)	2	0	2	0	0
MON 531 Cotton (MON-00531-6)	2	0	2	0	0
281-24-236 Cotton (DAS-24236-5)	0	0	0	0	2
3006-210-23 Cotton (DAS-21023-5)	0	0	0	0	2
MON 88913 Cotton (MON-88913-8)	2	0	0	0	0
GHB614 Cotton (BCS-GH002-5)	0	2	0	0	0
GHB119 Cotton (BCS-GH005-8)	1	0	2	2	0
T304-40 Cotton (BCS-GH004-7)	2	0	2	2	0
MON 88701 Cotton (MON-88701-3)	2	0	2	2	0
DAS-81910-7 Cotton (DAS-81910-7)	0	0	0	0	2
COT102 Cotton (SYN-IR102-7)	0	0	2	0	0
GHB811 Cotton (BCS-GH811-4)	0	2	0	0	0

Bonfini, L.

2021

Joint Research Centre

Contact information
DG JOINT RESEARCH CENTRE
Directorate F - Health, Consumers and Reference Materials
Food & Feed Compliance
European Union Reference Laboratory for GM Food and Feed
Via E. Fermi 2749, 21027 Ispra (VA) – Italy
Functional mailbox: JRC-EURL-GMFF@ec.europa.eu

EU Science Hub
https://ec.europa.eu/jrc

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Disclaimer

The screening proposals are based on *in silico* predictions and on information available to the authors on 22 October 2021. The completeness of this report is limited to this date. Further information on the EU authorisation of GM Food and Feed can be found on the GMO Register of the European Commission.

Acknoledgements

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Authors

Laura Bonfini

Abstract

Given the high number of GMOs currently authorised or whose authorisation is pending or has expired, it is necessary to implement an optimised strategy for screening food and feed samples in the EU market. The JRC GMO-Matrix web application, available on the website of the European Union Reference Laboratory for Genetically Modified Food and Feed (EURL GMFF), may help designing such strategies. This web application provides *in silico* e-PCR predictions of the GM events possibly detected by the EU reference methods in the GMOMETHODS database. By using the JRC GMO-Matrix application, the EURL GMFF proposes in this report, screening strategies for detecting all EU authorised GMOs in samples containing cotton, oilseed rape, maize, soybean or sugar beet. These proposals may contribute to the design of more efficient approaches for EU legislative enforcement and inspection control.

1. Purpose

Scope of this document is to provide a screening proposal for the efficient detection of EU authorised GMOs. The proposal is based on the EU authorisation status of the GM events as displayed on the Community Register of GM food and feed ([1]) on 22 October 2021 and by *in silico* analyses performed on the same date on the JRC GMO-Matrix application ([2]).

2. Introduction

Regulation (EU) No 2017/625 ([3]) states that the European Union Reference Laboratories (EURLs) for feed and food are responsible, amongst others, for "providing national reference laboratories with details and guidance on the methods of laboratory analysis, testing or diagnosis, including reference methods". To that end, the European Union Reference Laboratory for Genetically Modified Food and Feed (EURL GMFF) has developed a database of EU reference methods for GMO analysis, called "GMOMETHODS" ([4]) available at https://gmo-crl.jrc.ec.europa.eu/gmomethods/ (see Figure 1).

Figure 1. GMOMETHODS database home page

The database contains DNA-based detection methods that have been validated in a collaborative trial according to the principles and requirements of ISO 5725 ([5]) and/or the International Union of Pure and Applied Chemistry (IUPAC) ([6]) protocol or that have been verified by the EURL GMFF for EU legal purposes. These methods cover at least all the GMOs that have been authorised in the EU, or whose authorisation is pending or has expired.

The data outlined in Table 1 provide an overview on the methods included in the GMOMETHODS database up to 22 October 2021. The database offers information on 198 different polymerase chain reaction (PCR) methods covering 148 and 50 assays respectively for GMO and taxon detection. It includes 90 event-specific methods for identification of 86 single GM events, 35 'element-specific' screening assays and 23 'construct-specific' methods that in some instances can be used for screening purposes.

Table 1. GMO and taxon-specific methods included in the GMOMETHODS database according to specificity and purpose of the analysis

Target	Specificity	Purpose		Total
		Qualitative	Quantitative	
	Event-specific	12	78	90
GMO	Construct-specific	15	8	23
	Element-specific	31	4	35
Taxon	Species-specific	16	33	49
	Plant-specific	1	0	1
	Total methods	**75**	**123**	**198**

These screening assays allow detecting 20 single or combined genetic elements (see Table 2) used in the development of many GMOs approved worldwide [7].

Table 2. Screening targets detected by the EU reference methods

N	Screening Target	Abbreviation
1	Cauliflower Mosaic Virus 35S promoter	CaMV P-35S
2	*Cauliflower Mosaic Virus 35S* terminator	*CaMV T-35S*
3	*Cauliflower Mosaic Virus 35S* terminator from pCAMBIA vectors	*T-35SpCAMBIA*
4	*CP4 epsps* gene from *Agrobacterium tumefaciens* type I and II	*CP4-epsps*
5	*Cry1Ab/Ac* modified genes derived from *Bacillus thuringiensis*	*cry1Ab/Ac*
6	*Cry1A(b)* synthetic gene derived from *Bacillus thuringiensis*	*cry1A(b)*
7	*Cry1Ac* synthetic gene derived from *Bacillus thuringiensis*	*cry1Ac*
8	*E9* terminator from *Pisum sativum*	*T-E9*
9	*Figwort Mosaic Virus 35S* promoter	*P-FMV*
10	Junction region between the *Cauliflower Mosaic Virus 35S* promoter and the Phosphinothricin N-acetyl transferase gene from *Streptomyces hygroscopicus*	*CaMV P-35S_bar*
11	Junction region between the *Cauliflower Mosaic Virus 35S* promoter and the Phosphinothricin N-acetyl transferase gene from *Streptomyces viridochromogenes*	*CaMV P-35S_pat*
12	Junction region between the chloroplast transit peptide 2 sequence from the *Arabidopsis thaliana epsps* gene and the *CP4 epsps* gene from *Agrobacterium tumefaciens*	*CTP2_CP4 epsps*
13	Junction region between the *cry1Ab/Ac* modified genes and DNA spacer sequences	*cry1Ab/Ac_ DNA spacer*
14	Junction region between the maize ubiquitin promoter and the *cry1Ab/Ac* modified genes	*P-ubi_cry1Ab/Ac*
15	Junction region between the nopaline synthase promoter from *Agrobacterium tumefaciens* and the neomycin phosphotransferase II gene	*T-nos_nptII*
16	Neomycin phosphotransferase II gene	*nptII*
17	Nopaline synthase promoter from *Agrobacterium tumefaciens*	*P-nos*
18	Nopaline synthase terminator from *Agrobacterium tumefaciens*	*T-nos*
19	Phosphinothricin N-acetyl transferase gene from bacterium *Streptomyces hygroscopicus*	*bar*
20	Phosphinothricin N-acetyltransferase gene from bacterium *Streptomyces viridochromogenes*	*pat*

According to *in silico* analyses performed on 22 October 2021 on the JRC GMO-Matrix ([2]) application (see Figu*re 2*) available on the EURL GMFF website these screening methods may allow detecting 94 % (58/62) of the single GM events currently authorised in the EU ([i]) or for which the authorisation procedure is pending or has expired. Only four GM events could not be detected *in silico* by screening EU reference methods currently included in the GMOMETHODS database; these were maize DAS-40278-9, oilseed rape 73496 and the two soybean events 305423 and CV127. Detection for these events can be achieved by using only the respective event-specific methods.

Figure 2. JRC GMO-Matrix output example

	QL-ELE-00-012 (CaMV P-35S)	QT-CON-00-008 (OTP-mEPSPS)	QL-ELE-00-013 (T-nos)	QL-ELE-00-026 (bar)	QL-ELE-00-025 (pat)
LLCotton25 Cotton (ACS-GH001-3)	2	0	2	2	0
MON 1445 Cotton (MON-01445-2)	2	0	2	0	0
MON 15947 Cotton (MON-15985-7)	2	0	2	0	0
MON 531 Cotton (MON-00531-6)	2	0	2	0	0
281-24-236 Cotton (DAS-24236-5)	0	0	0	0	2
3006-210-23 Cotton (DAS-21023-5)	0	0	0	0	2
MON 88913 Cotton (MON-88913-8)	2	0	0	0	0
GHB614 Cotton (BCS-GH002-5)	0	2	0	0	0
GHB119 Cotton (BCS-GH005-8)	1	0	2	2	0
T304-40 Cotton (BCS-GH004-7)	2	0	2	2	0
MON 88701 Cotton (MON-88701-3)	2	0	2	2	0
DAS-81910-7 Cotton (DAS-81910-7)	0	0	0	0	2
COT102 Cotton (SYN-IR102-7)	0	0	2	0	0
GHB811 Cotton (BCS-GH811-4)	0	2	0	0	0

[i] GM food and feed authorised under Regulation (EC) No 1829/2003

3. Screening strategy proposal for detecting EU authorised GMOs

The GMOMETHODS database offers in several cases more than one assay for the detection of a GMO or a target genetic element. Given the high number of GMOs currently authorised or whose authorisation is pending or has expired, it is necessary to implement an optimised strategy for screening food and feed samples in the EU market. Screening approaches should provide maximal coverage, best performance and minimal cost and laboratory workload. Ideally, they could include additional methods for further discriminating the GM events possibly detected in the sample. The JRC GMO-Matrix ([2]) application developed by the JRC may help designing such strategies since it provides *in silico* e-PCR predictions of the GM events possibly detected by the EU reference methods. The computer simulations are performed using primers and probe sequences from the GMOMETHODS database and GMOs sequences from a JRC internal database. The latter includes sequences provided by the applicants for authorisation of GMOs or retrieved independently from nucleotide/patent databases. The scripts that simulate PCR amplification use "re-PCR" (Rotmistrovsky et al., 2004) ([8]) for detecting potential amplicons in GMO sequences and "matcher" from the EMBOSS package (Rice et al., 2000) ([9]) for verifying probe annealing when the method contains one. An analysis of the *in silico* results can highlight, in principle, which methods could be used for detecting a maximal spectrum of authorised GM events for each host species. To that purpose, a bioinformatics analysis was performed on the JRC GMO-Matrix application on 22 October 2021. As a result, Tables 3-7 propose screening strategies for detecting all EU authorised GMOs[ii] in samples containing respectively cotton, oilseed rape, maize, soybean and sugar beet. The proposals employ only EU reference methods from the GMOMETHODS database to ensure consistent and reproducible results in the analyses and cover many assays that are already included on the JRC Pre-Spotted-Plates (PSPs)[10]. They are based on *in silico* predictions and on information available on 22 October 2021 and are limited for their completeness to this date. A rationale for the methods selection is provided in the Annex of this document.

In the tables below the methods necessary for detecting for each species all EU authorised GMOs are highlighted in dark blue color, while those that could further discriminate the possible events present in a sample are presented in a lighter blue shade. Methods that are components of a multiplex PCR are combined under the same heading specifying the type of PCR assay. The target genetic element is displayed in red beneath the code of the related EU reference method. In each column, the GMOs that could be detected by the corresponding method are listed in alphabetical order. Their status of authorisation as of 22 October 2021 is highlighted by different colors: green (EU authorised), light green (pending EU authorisation), yellow (subject to a Commission Decision on withdrawal from the EU market) and orange (expired EU authorisation). GMOs for which a detection method has been validated by the EURL GMFF but that are not falling under Regulation (EU) No 619/2011 are marked in bold green text while GMOs that are not authorised in the EU are displayed in normal black characters.

Table 3. Screening proposal for EU authorised GM cotton events

Duplex PCR		Duplex PCR		Simplex PCR	Simplex PCR
QL-ELE-00-012 P-35S	QL-ELE-00-013 T-nos	QL-ELE-00-025 pat	QL-ELE-00-026 bar	QT-CON-00-008 OTP-mEPSPS	QL-ELE-00-024 tE9
		281-24-236			
		3006-210-23			
	COT102				
		DAS-81910-7			
	GHB119		GHB119		
				GHB614	
				GHB811	
LLCotton25	LLCotton25		LLCotton25		
MON 1445	MON 1445				MON 1445
MON 15985	MON 15985				
MON 531	MON 531				
MON 88701	MON 88701		MON 88701		
MON 88913					MON 88913
T304-40	T304-40		T304-40		

[ii] GMOs authorised under Regulation (EC) No 1829/2003

Table 4. Screening proposal for EU authorised GM maize events

Duplex PCR		Simplex PCR	Duplex PCR	
QL-ELE-00-012 P-35S	QL-ELE-00-013 T-nos	QT-EVE-ZM-004 DAS-40278-9	QL-ELE-00-025 pat	QL-ELE-00-026 bar
1507			1507	
32			32	
32316			32316	
	3272			
4114			4114	
	5307			
59122			59122	
98140				
Bt11	Bt11		Bt11	
Bt176*				Bt176*
		DAS-40278-9		
	GA21			
	MIR162			
	MIR604			
MON 810				
MON 863*	MON 863*			
MON 87403				
MON 87411				
			MON 87419	
MON 87427	MON 87427			
MON 87429			MON 87429	
MON 87460	MON 87460			
MON 88017	MON 88017			
MON 89034	MON 89034			
MZHG0JG	MZHG0JG		MZHG0JG	
MZIR098	MZIR098		MZIR098	
NK603	NK603			
T25			T25	

* GMOs also included in the list of products subject to a Commission Decision on withdrawal from the EU market

Table 5. Screening proposal for EU authorised GM oilseed rape events

Duplex PCR		Simplex PCR	Simplex PCR
QL-ELE-00-012 P-35S	QL-ELE-00-013 T-nos	QL-ELE-00-024 tE9	QT-EVE-BN-009 73496
			73496
		GT73	
		LBFLFK (insert 1)	
		LBFLFK (insert 2)	
		MON 88302	
	MS1		
	MS11		
	MS8		
Oxy-235	Oxy-235		
	RF1		
	RF2		
	RF3		
T45			
Topas 19/2			

Table 6. Screening proposal for EU authorised GM soybean events

Duplex PCR		Simplex PCR	Simplex PCR	Duplex PCR		Simplex PCR	Simplex PCR
QL-ELE-00-012 P-35S	QL-ELE-00- 013 T-nos	QL-ELE-00-016 Cry1Ab/Ac	QL-ELE-00- 024 tE9	QL-ELE-00- 025 pat	QL-ELE-00-026 bar	QT-EVE-GM-008 305423	QT-EVE-GM-011 CV127
						305423	
356043							
40-3-2	40-3-2						
A2704-12				A2704-12			
A5547-127				A5547-127			
							CV127
				DAS-44406-6			
				DAS-68416-4			
				DAS-81419-2			
	FG72						
GMB151*							
HB4	HB4				HB4		
		MON 87701					
			MON 87705				
			MON 87708				
		MON 87751					
			MON 87769				
			MON 89788				
SYHT0H2	SYHT0H2			SYHT0H2			

* The primers and probes of the QL-ELE-00-012 method provide experimentally a positive amplification product even if *in silico* do not perfect anneal to their target in the GM event GMB151.

Table 7. Screening proposal for EU authorised GM sugar beet events

Simplex PCR
QL-ELE-00-024 tE9
H7-1
GTSB77

Legend

	GMOs authorised in the EU
	GMOs with pending authorisation in feed fulfilling the requirements of Regulation (EU) No 619/2011
	GMOs with an expired authorisation
	GMOs subject to a Commission Decision on withdrawal from the market
XXXXX	GMOs for which a detection method has been validated by the EURL GMFF but not falling under Regulation (EU) No 619/2011
XXXXX	GMOs not authorised in the EU

4. Conclusions

It can be noticed that for some crops, two or three screening methods are sufficient for detecting all related authorised GMOs. For other crops, up to seven methods are necessary for a complete coverage, and in some instances, event-specific methods are additionally needed for detecting GMOs not covered by the screening assays. The analytical approaches that are proposed in the tables offer the minimal number of methods for detecting all EU authorized GMOs in each species. The employment of additional screening methods in the testing strategy may provide further discriminatory capacity especially in feed but may not be sufficient for uniquely identifying the GM events present in a sample.

In the tables some unauthorised GMOs detected by the EU reference methods are also indicated. Their list however, is not exhaustive since the JRC GMO-Matrix does not include *in silico* e-PCR predictions for all GMOs developed or commercialised worldwide. The presence of a non-authorised GMO can be generally presumed when the screening results differ from those expected for the EU authorised events finally identified in the sample. Nevertheless, the incidence of a non-authorised GMO can be masked by the concomitant presence of an authorised GMO presenting similar screening elements. The presence of non-authorised GM events in the food or feed samples analysed, therefore, cannot be formally excluded.

Some sequences targeted by the screening methods are derived from organisms that may be naturally present in food and feed samples and may therefore produce false positive results. It is therefore important to test the food and feed samples in parallel with PCR methods specific for those donor organisms (i.e. for the occurrence of the *Cauliflower Mosaic Virus (CaMV)* in samples containing ingredients from *Brassicaceae* or for contamination by *Agrobacterium* species in samples resulting positive to nopaline synthase (*nos*) terminator assays. Since the E9 terminator (*tE9*) element present in many GM events is derived from the pea genome, a method targeting a pea endogenous gene (i.e. *lectin*) may also be used in parallel with the E9 assay to exclude the presence of pea derived products in the sample.

These screening proposals may be more efficient in enforcing EU GMO legislation and may promote better harmonisation in the analyses of official control laboratories. Finally, the use of EU reference methods from the GMOMETHODS database following internationally accepted standard protocols may allow global applicability of safety and trade issues.

List of abbreviations and definitions

Abbreviations

CaMV	Cauliflower Mosaic Virus
ENGL	European Network of GMO Laboratories
EPSPS	5-enolpyruvylshikimate-3-phosphate synthase
EU	European Union
EURL	European Union Reference Laboratory
EURL GMFF	European Union Reference Laboratory for Genetically Modified Food and Feed
GM	Genetically Modified
GMO	Genetically Modified Organism
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
Nos	Nopaline synthase
PCR	Polymerase Chain Reaction
PSPs	Pre-Spotted-Plates
JRC	Joint Research Centre

Definitions

Qualitative method	method of analysis whose response is either the presence or absence of the target DNA sequence(s) in a sample.
Quantitative method	method of analysis whose response is the quantity of the target DNA sequence(s) in a sample.
Event-specific method	method that targets a sequence unique to a single genetic modification event (i.e. the fusion sequence composed of the terminal base pairs of the inserted DNA and the adjacent base pairs of the recipient host genome at the insertion locus).
Construct-specific method	method that targets an inserted DNA sequence composed of at least two elements that do not naturally co-exist in this conformation, and where the 5' and 3' end of the sequence are derived from two separate elements.
Element-specific method	method that targets a single discrete DNA sequence such as a promoter, a terminator, an intron or the coding part of a gene.
Species-specific method	method that detects a sequence known to be specific for the target species.
Plant-specific method	method that detects a sequence know to be specific for the plant kingdom.

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Annex

Annex 1. Rationale for the screening proposal

The screening approaches proposed were determined following the criteria of maximal coverage, best performance and minimum laboratory workload. They are based on the results of *in silico* analyses performed on the JRC GMO-Matrix application on 22 October 2021. A rationale is provided below for the selection of the genetic targets and corresponding EU reference methods.

Most of these methods are already implemented on the Pre-Spotted Plates (PSPs) developed by the JRC for performing GMO screening analyses. To reduce laboratory workload, two duplex assays for detecting respectively the P-35S/T-nos and pat/bar elements have been selected in place of the single methods used on the PSPs. The primers, probes and amplification conditions for targeting the P-35S and T-nos elements in the duplex assay are identical to those of the single methods included on the PSPs. The primers and probes targeting the bar element in the second duplex assay are also identical to the method included on the PSPs while those for the pat element are different. Both duplex methods could be considered in line with the minimum performance requirements defined in the ENGL document and in particular, with the practicability condition setting the maximum volume of the PCR reactions to 25 µL. To note that the primers and probes of the P-35S method provide experimentally a positive amplification product also with the GM event GMB151 even if *in silico* they do not perfectly anneal to their target.

The method **QL-ELE-00-016** targeting the Cry1Ab/Ac sequences is included in the proposal to allow detection of soybean GM events MON 87701 and MON 87751. This method is also included on the PSPs. The only other EU reference method (QL-ELE-00-020) detecting these soybean events was not selected because it is using a SYBR Green approach for amplicon detection.

The **QT-CON-00-008** method targeting the junction between an optimised transit peptide sequence and the point-mutated *epsps* gene from maize (CTP2-CP4EPSPS) is included in the proposal for detecting the cotton GM events GHB614 and GHB811. These events are not detected *in silico* by any other screening method.

The **QL-ELE-00-024** method targeting the tE9 element is included in the proposal for detecting GM sugar beet H7-1, oilseed rape GT73 and MON 88302 and soybean events MON 89788, MON 87769, MON 87705 and MON 87708. All these events are only partially covered by the methods QL-CON-00-008 (included on the PSPs), QL-ELE-00-010 and QL-ELE-00-015, which do not detect soybean events MON 87769 and MON 87708.

The event-specific method **QT-EVE-ZM-004** targeting maize DAS-40278-9 is included in the proposal because the event is not detected *in silico* by any screening EU reference method.

The event-specific method **QT-EVE-BN-009** targeting oilseed rape 73496 is included in the proposal because the event is not detected *in silico* by any screening EU reference method.

The event-specific methods **QT-EVE-GM-008** and **QT-EVE-GM-011** targeting respectively soybean 305423 and CV127 are included in the proposal because these events are not detected *in silico* by any screening EU reference method.

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