External Scientific Report

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OECD MetaPath
Incorporation of Pesticide Residue Data

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Abstract

In order to support the data submission and regulatory review of pesticide residue data in the remit of active substance and MRL assessments, the German Federal Institute for Risk Assessment (BfR) as contractor to EFSA has prepared a Final Scientific Report focusing on the data extraction and coding of pesticide metabolism studies.

In total 1265 metabolic maps have been coded by BfR from plant, livestock and rotational crop metabolism studies and successfully been validated by the project partner ANSES.

Key words: MetaPath, Metabolism study, MSS Composer, Metabolic Pathway, Pesticide Residue

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Summary

In order to support the data submission and regulatory review of pesticide residue data in the remit of active substance and MRL assessments, EFSA has launched a tender project for extraction of metabolism data from plant and livestock metabolism studies with pesticide active substances and their entry into the MetaPath system. The German Federal Institute for Risk Assessment (BfR) as the contractor has prepared an External Scientific Report, which details the final achievements, methodology applied, and suggested improvements.

The tasks under Framework Contract OC/EFSA/PRES/2019/01 requires data extraction/collection and entry, import or drawing of chemical structures and generation of xml-files by MSS Composers for - in total - 1350 metabolism pathway maps.

The deliverables are considered as adequately and timely submitted by BfR. A number of 1265 metabolic maps have been coded by BfR from plant, livestock and rotational crop metabolism studies, and successfully been validated by the project partner ANSES.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

This contract was awarded by EFSA to: German Federal Institute for Risk Assessment

Contractor/Beneficiary: German Federal Institute for Risk Assessment

Contract title: OECD MetaPath- Incorporation of Pesticide Residue Data

Contract number: OC/EFSA/PRES/2019/01

In order to support the data submission and regulatory review of pesticide residue data in the remit of active substance and MRL assessments and to increase the data base underlying the pesticide dietary and non-dietary risk assessments, EFSA has launched the tender project "OECD Metapath — Incorporation of Pesticide Residue Data" (in the following called `project´) for extraction of metabolism data from plant and livestock metabolism studies with pesticide active substances and their entry into the MetaPath system.

MetaPath is a relational and searchable database developed by the Laboratory of Mathematical Chemistry (LMC) Burgas (Bulgaria) and the U.S. E.P.A., which includes an embedded set of data evaluation tools that can be applied to different discrete data sets. Within the area of pesticides, the MetaPath system currently stores meta data of rat, plant and livestock metabolism studies, and allows inter alia the identification of similar metabolites or substructures from different active substances, the display of overlapping metabolic pathways within and across different taxa or regulatory defined groups. Efficient search strategies thereby allow not only the setup of cumulative exposure scenarios involving different pesticide active substances, but may also enable an advanced toxicological read-across, thus reducing the need for additional vertebrate studies. The systematic and integrated use of available regulatory metabolism data via the MetaPath pesticide database is considered a great improvement for informed pesticide risk assessments.

The German Federal Institute for Risk Assessment (BfR) as the contractor of EFSA for this project has prepared this Final Scientific Report to satisfy the requirements expressed under point 1.3. of the Tender Specifications (´TASKS, DELIVERABLES, TIMELINE AND PAYMENTS`). Results of interim reports have been integrated in the final report.

1.2. Terms of Reference as provided by the requestor

Overall objective:

The overall objective of the contract resulting from the present call for tenders is extraction and entry of data from studies with pesticide active substances and their metabolites in plants and livestock in order to generate a specific and functional database for the MetaPath system. Such a database would be a practical tool to support regulatory assessments conducted by the EFSA Pesticides Residue (PRES) and Peer Review (PREV) Units in collaboration with Member State authorities and, as part of a collaborative OECD project, by the international community of regulatory assessors connected in the MetaPath Users Group. The database would also complement existing in silico tools in the OECD QSAR toolbox and present possibilities to explore and routinely implement advanced risk

assessment methodologies. To put this vision into practice, a pre-defined minimum set of data (Annex A) has to be collected and entered in a structured format and metabolism pathways maps be generated from that information for a representative number of pesticide active substances and their metabolites assessed by ESFA in the past. The number of created metabolism pathway maps envisaged by this project is approx. 1200 to 1350. To automate the data entry works, customised screen editors called MSS Composers are available and xml files will be created with this software. Before importation of the xml data into the regulatory database shared by the OECD MetaPath Users Group, data entry and mapping will be subject to a final quality check by a third party commissioned by EFSA to ensure error-free functioning of the MetaPath system upon data import.

Specific objective 1: Extraction of information from metabolism studies with pesticide active substances or their metabolites in plant and livestock and entering in a structured format using a software

The respective data extraction should cover information on the active substances and their metabolites reported in the pesticide dossiers submitted for registration under Directive 91/414/EEC (Annex II, points 6.1, 6.2 and 6.5) or Regulation (EC) No 1107/2009 in line with the applicable data requirements (Regulation (EU) No 544/2011 Annex Part A, points 6.1, 6.2, 6.6 or Regulation (EU) No 283/2013, Annex Part A, points 6.2. and 6.6.1) for metabolism studies in plant and livestock. Upon request, additional metabolism data, if available and submitted for the assessment of MRLs under Reg. (EC) No 396/2005 and evaluated by EFSA should also be considered.

The following information should be collected and entered in a structured format using the MSS Composers software in order to generate xml files. Annex 3 of this call (Annex A) contains a list indicating the minimum information to be extracted and entered in the MSS Composers software. In addition, the import and/or drawing and mapping of chemical structures is required. A Standard Operating Procedure (SOP) for obtaining and extracting the information from study reports in the registration dossiers and relevant supporting documentation, such as e.g. executive summary reports or Assessment Reports, plus an appropriate quality control protocol for the data entry should be provided by the contractor, which will be subject to approval by EFSA during the kick-off meeting.

Studies and information considered as relevant will be identified by EFSA and the references communicated to the contractor as batch assignments. In exceptional cases, such as for studies considered relevant and only submitted for the assessment of MRLs under Reg. (EC) No 396/2005, EFSA may provide the study report to the contractor. To perform the work necessary under this contract, the contractor must be able to independently locate and have access to the relevant metabolism study reports in a given pesticide dossier submitted for registration, their executive summaries and the relevant supporting information. EFSA will not provide access to such information.

Objective 2 : External scientific report

To conclude the project, the contractor will be required to draft an External Scientific Report about the methodology applied, the final achievement, the 'lessons learned' during the project, and including observations and suggestions for improvements with regard to the software or potential efficiency increase of the data collection and entry procedures as

appropriate, including templates, data spreadsheets or applications developed by the tenderer. The information will be valuable for potential future projects to generate structured data or work with the MetaPath system. The External Scientific Report will be published.

2. Data and Methodologies

2.1. Data

The references of 1226 metabolism studies including their complementing reports (e.g. Addenda, field or lab parts, amendments etc)[1] have been provided by EFSA for coding under Order Forms 1, 2 and 3. The references refer to 169 pesticide active substances or their metabolites as parent compounds. A short list of active substances and the study types is given in Table 1.

2.2. Methodologies

The studies were processed according to a Standard Operating Procedure (SOP), which integrates the manuals provided by the French Authority ANSES in the frame of this project2. This SOP describes how relevant information is obtained and extracted from plant and livestock metabolism studies with Metabolism Study Summary (MSS) Composers, and how internal quality control is implemented in the process. The SOP (rev.1 of 27 Jan 2020) addresses requirements set under Objective 1 of EFSA´s Tender Specifications and takes up the consensus of all project partners (EFSA, BfR, ANSES) on adequate coding including reduced data entries.

The applied coding practice has been continuously improved based on internal (BfR) and external (ANSES) peer-reviews with detailed reporting of coding errors, inconsistencies, assumed incompleteness of information and typos, and taking up recent developments of the software package.

2.2.1. Receipt, registration and filing of documents (step 1)

All project related documents (e.g. tender documentation including list of minimum requirements for extraction; list of active substances to be extracted; standard operating procedure; communication with EFSA and external reviewers, list of studies to be coded) were electronically registered and filed.

EFSA has sent various lists of studies for coding under Order Form 1 (targeted 337 maps, till 31 August 2020), Order Form 2 (further 338 maps, 01/09/20 to 15/06/21) and Order

2.2.2. Study identification and completeness check (step 2)

The existing unique BfR-study identifiers (eASB numbers) for each metabolism study have been attributed to the metabolism studies included in the list of active substances for extraction.

[1] Refers to BfR references, which might deviate due to BfR specific referencing of addenda, supplements etc.

https://www.efsa.europa.eu/sites/default/files/2021-03/mss-composers-manual.pdf

Metabolism studies exclusively evaluated by EFSA in the context of MRL assessments (Reg. (EC) No 396/2005) and not previously submitted to BfR in any regulatory context were identified, and upon request of BfR, EFSA provided the missing study reports.

2.2.3. Advanced training and harmonisation of expertise (step 3)

All members of the project group plus additional scientists from BfR Pesticides Safety Department took part in an initial two day advanced training session in order to harmonise the experts knowledge in all areas relevant to the project:

1. Project requirements according to tender specifications (tasks, deliverables, timelines);
2. Presentation of project organisation; software supported management (OpenProject©) to monitor the project development and accordingly to specify the individual work to be done;
3. Insight in the structure and contents of relevant OECD Technical Guidelines (OECD TG 501, 502, 503);
4. Functioning of MSS Composer software and minimum information to be extracted and entered;
5. Familiarity with MSS Composer manuals and SOP;
6. Internal quality assurance measures.

Constant trainings on new software releases, mutual exchange within BfR group members, internal cross-validation of files and review by external partners (ANSES) guaranteed quality assured coding of studies.

2.2.4. Allocation of work (step 4)

All data extraction work (read-out of study information, completion of MSS Composer spreadsheets, technical verification of proper extraction) were done by each of the scientific experts. Responsibilities were set and sets of metabolism studies with identical and related chemical structures of residues were attributed to individual scientific experts in order to use economies of scale. Re-arrangements of selection and attribution of active substances were managed by group members to account for unforeseen incidences e.g. during COVID 19 crisis or due to personnel turnover during the project.

2.2.5. Extraction and coding of data in MSS Composers (step 5)

Each scientific expert of the project group was assigned a list of studies to be extracted by the project leader. Original studies were used as primary source for extraction, while study summaries from EU Assessment Reports (DAR, RAR) or EFSA Reasoned Opinions were only consulted for necessary clarifications. Data extraction and entering into MSS Composers to develop the metabolic maps was performed using the most recent template (MSS Composer for plant, livestock, rotational crop) according to the technical manuals and considering all relevant fields as indicated in Annex 3 of the Tender Specifications (´Fields in MSS Composers for data input´ Annex A). The latest release of MetaPath software package during the terminal phase of the project (March 2022), which allows coding of generic chemical structures, has not been used by the contractor in order to maintain

consistency within the data base, that has been coded so far. This point has been communicated to the project partners.

All scientific experts actively identified sources of improvements in the procedure and of potential efficiency measures.

2.2.6. Internal validation (step 6)

An internal quality control protocol for data extraction and entry including drawing of chemical structures and generation of xml files has been applied.

2.2.6.1. Technical validation (step 6a)

The scientific expert is responsible for the technical validation of XML-files at the end of the coding process. Validation is performed by uploading the generated XML-file in the local MetaPath data base in order to verify the proper functioning of syntax. Only in case of successful upload, the extracted data is forwarded for validation of contents.

2.2.6.2. Validation of contents (step 6b)

Upon upload of XML-files to the local MetaPath data base, the project leader validates the extracted contents for the following criteria:

1. Completeness of study information according to Annex 3 of Tender Specification (Annex A)
2. Correctness of general information
3. Correctness of chemical structures

2.2.7. Dispatch of data to external reviewer and EFSA (step 7)

All XML-files that passed the internal validation procedure were forwarded as batch to the external reviewer on a biweekly basis. Exchange of xml-files was realised via EFSA´s Sharepoint platform, and the progress of coding and validation reported in the accompanying spreadsheet.

2.2.8. Feed-back and corrective actions (step 8)

The project leader co-ordinated the generation of XML-files according to the proposed methodology and their dispatch to third party reviewers. The external reviewers informed the project team on the outcome of external validation and, if required, necessary amendments within two weeks. A respective folder structure has been set up at EFSA Sharepoint, where BfRs submissions (version 1/v1) and re-submissions (v3, v5) were filed, as well as ANSES´ review reports and files (v2, v4, vf).

2.2.9. Reporting (step 9)

Reports have been provided to EFSA for Order Form 1 and 2, as well as for Order Form 3 (Interim reports 3/1, 3/2, and 3/3). This Final External Scientific Report contains, according to the provisions of the Tender Specifications, the methodology applied, the final achievements, the 'lessons learned' during the project, and recommendations.

2.2.10. Justification for the proposed methodology

The proposed methodology is considered to allow a transparent and efficient way of data extraction, coding and quality control ensuring to keep the timelines set.

Coding follows the long-term practice of extracting and entering information using MSS Composers. The manuals for coding were developed on previous coding experiences by the French authority ANSES and by U.S. E.P.A.

The software supported project management allows executing, controlling, and finalising of the project to achieve the goals and meet the objectives 1 (Extraction of information) and 2 (external scientific report) within the given timelines.

2.3. Co-operation with project partners

Co-operation with all project partners (EFSA, ANSES) remained excellent over the whole phase. Exchange of files and related informations via Sharepoint and communication went smooth and within short time-frames.

2.4. Compliance to timelines

Timelines for all deliverables under Order Forms 1 to 3 have been met. Due to force majeur during COVID19 crisis, EFSA and the contractor agreed to extent the initially set timelines for OF1 and OF2 by 2 months and by 6 weeks, respectively.

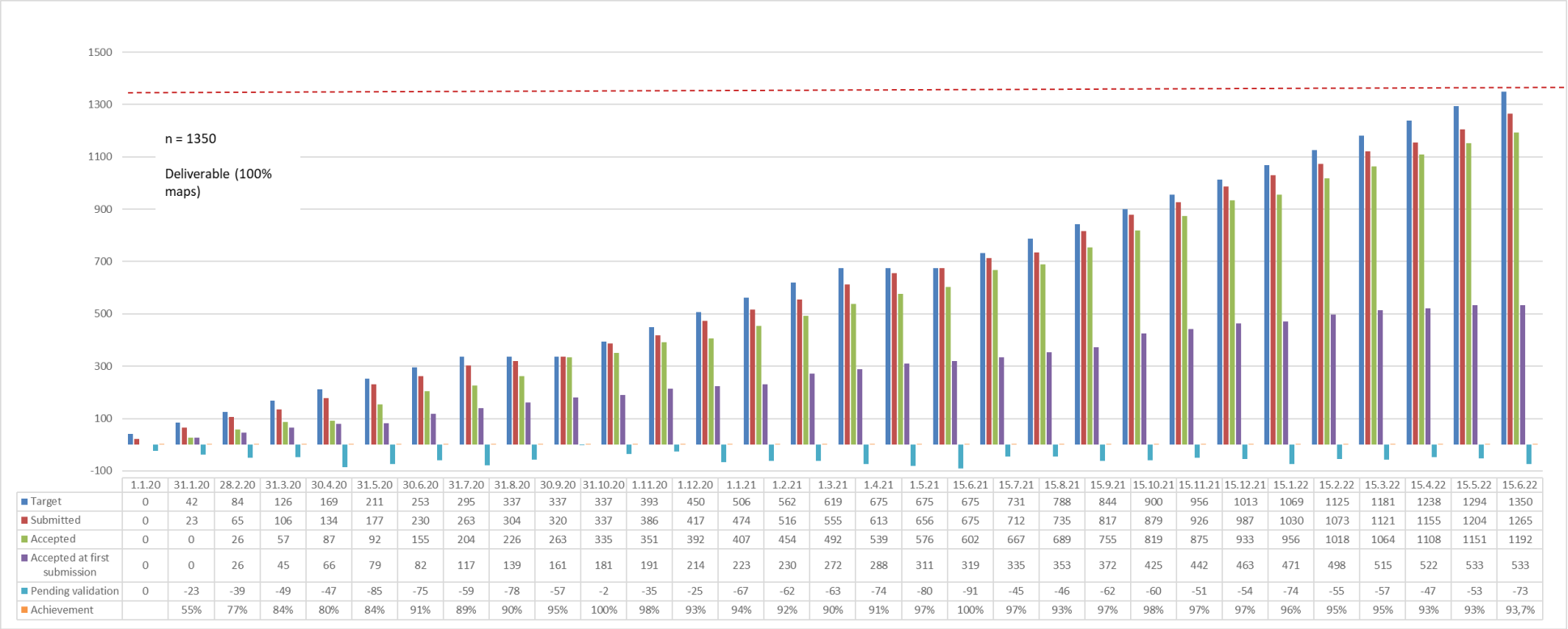
3. Results

3.1. Generation of MSS-Composer files

EFSA has provided a list of metabolism studies from 169 active substances and metabolites to the contractor over the whole project phase. in total, 1265 metabolic maps have been coded from these plant, livestock and rotational crop metabolism studies and provided to project partners via the sharepoint platform as xml-files. The progress of coding over the whole project is shown in figure 1.

The maps have been approved by the project partner ANSES as a true representation of the relevant study information, with a level of detail and format according to the consensus reached between all project partners, and with full functionality of the generated xml-files in the MetaPath software.

Out of the 1265 maps, 630 maps were coded from plant metabolism studies, 368 from rotational crop studies, and 267 from livestock metabolism studies (Figure 2). The crop groups as defined in OECD TG 501 are covered by the data base to a different extent: 185 maps refer to the ´Fruit´ category, 174 to ´Cereal/Grass crops, 100 to ´Root crops´, 114 to ´Pulses and oilseeds´, 47 to ´Leafy crops, and 10 to the ´Miscellaneous´crop category.



	1.1.20	31.1.20	28.2.20	31.3.20	30.4.20	31.5.20	30.6.20	31.7.20	31.8.20	30.9.20	31.10.20	1.11.20	1.12.20	1.1.21	1.2.21	1.3.21	1.4.21	1.5.21	15.6.21	15.7.21	15.8.21	15.9.21	15.10.21	15.11.21	15.12.21	15.1.22	15.2.22	15.3.22	15.4.22	15.5.22	15.6.22
Target	0	42	84	126	169	211	253	295	337	337	337	393	450	506	562	619	675	675	675	731	788	844	900	956	1013	1069	1125	1181	1238	1294	1350
Submitted	0	23	65	106	134	177	230	263	304	320	337	386	417	474	516	555	613	656	675	712	735	817	879	926	987	1030	1073	1121	1155	1204	1265
Accepted	0	0	26	57	87	92	155	204	226	263	335	351	392	407	454	492	539	576	602	667	689	755	819	875	933	956	1018	1064	1108	1151	1192
Accepted at first submission	0	0	26	45	66	79	82	117	139	161	181	191	214	223	230	272	288	311	319	335	353	372	425	442	463	471	498	515	522	533	533
Pending validation	0	-23	-39	-49	-47	-85	-75	-59	-78	-57	-2	-35	-25	-67	-62	-63	-74	-80	-91	-45	-46	-62	-60	-51	-54	-74	-55	-57	-47	-53	-73
Achievement		55%	77%	84%	80%	84%	91%	89%	90%	95%	100%	98%	93%	94%	92%	90%	91%	97%	100%	97%	93%	97%	98%	97%	97%	96%	95%	95%	93%	93%	93,7%

Figure 1: Progress of coding (Order Forms 1 to 3; as at 2022/06/15)

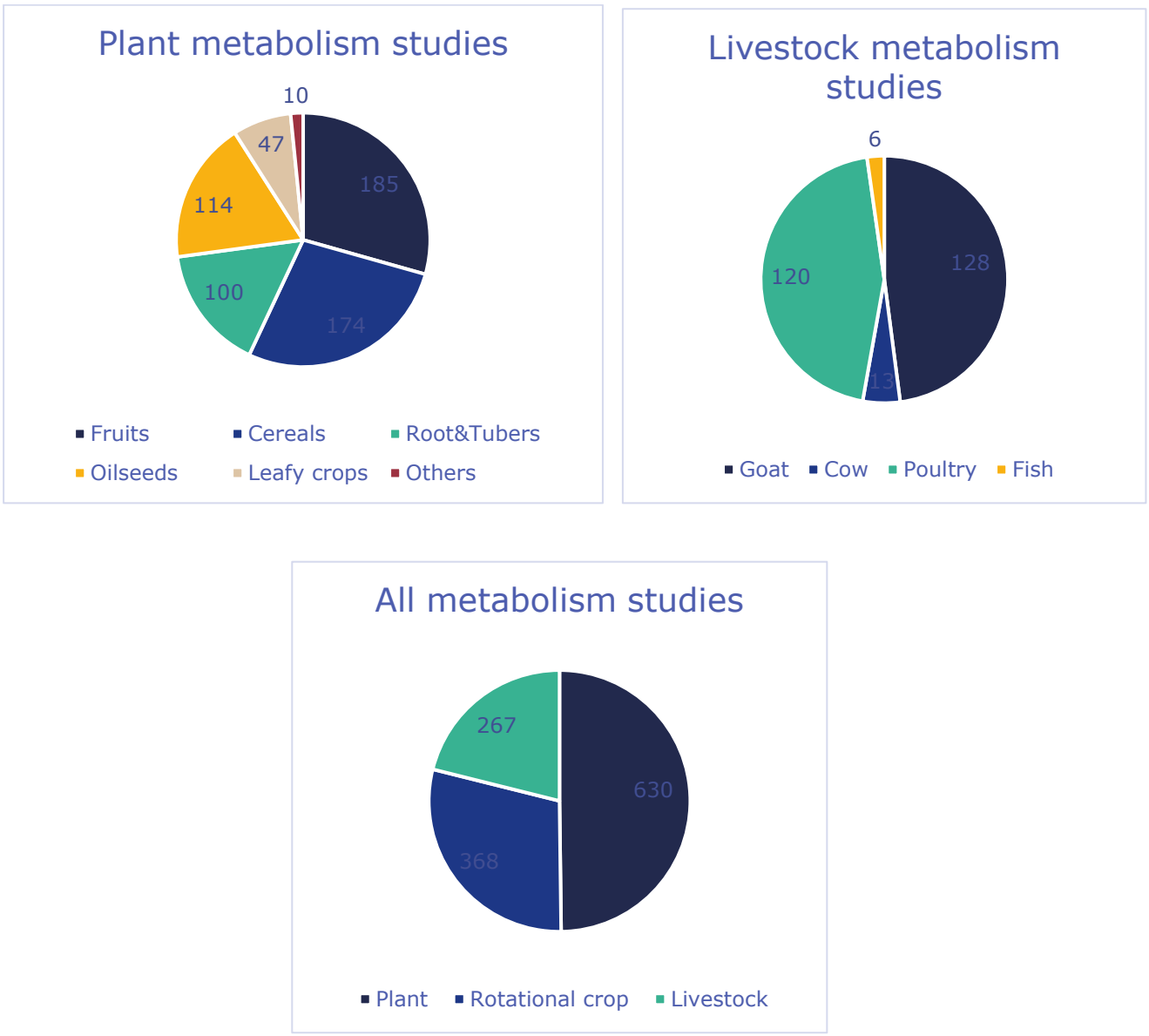


Figure 2: Metabolic maps of the residue metabolism studies and their distribution to different OECD categories.

The number of metabolic maps in the different categories and their attribution to individual active substances is shown in Table 1.

Table 1: Number of coded metabolic maps for active substances, sorted according to OECD TG 501, TG 502, and OECD TG 503

Active substance name (trivial)	Sum of maps	Fruit	Root crops	Leafy crops	Pulses & oilseeds	Cereal/ Grass crops	Miscellaneous	Rotational crops	Ruminant	Poultry	Fish
1,3 dichloropropene	3	2								1	
1,4-dimethylnaphtalene	4		2						1	1	
2,4 DB	5				1	1	1		1	1	
4-Hydroxy-2,5,6-Trichloroisophtalonitrile	1									1	
6-Benzyladenine	1	1									
Abamectin	6	3	1		1				1		
Acequinocyl	3	3									
Acetamiprid	9	2		3	1			3			
Acibenzolar-S-methyl	9	1		1		1	1	3	1	1	
Alpha-cypermethrin	11	2		1		3			2	2	1
Ametoctradin	8	1	1	1				3	1	1	
Amidosulfuron	13				1	1		9	1	1	
Aminopyralid	2					2					
Amisulbrom	7	2						3	1	1	
Asulam	7			4		1			1	1	
Benalaxyl	4	1						3			
Bentazon (6-OH)	2								1	1	
Bentazon (8-OH)	1									1	
Bentazon	9		2		1	3			2	1	
Benthiavalicarb	4	2	2								
Beta-cyfluthrin	4		2						1		1

Active substance name (trivial)	Sum of maps	Fruit	Root crops	Leafy crops	Pulses & oilseeds	Cereal/ Grass crops	Miscellaneous	Rotational crops	Ruminant	Poultry	Fish
Beta-cypermethrin	2					1			1		
Bifenazate	6	3	1		1	1					
Bifenthrin	5	1			1				2	1	
Bispyribac-sodium	5					3			1	1	
Bixafen	6	2	2							2	
Boscalid	6	1		1	1			3			
Bromuconazole	8	2				2		2	1	1	
Captan	14	5						4	3	2	
Carfentrazone-ethyl	2					2					
Chlorothalonil	12	1	2	1				6	1	1	
Chlorotoluron	6					1		3	1	1	
Chlorpropham	9		3	3					2	1	
Chlorpyriphos	2	1		1							
Chromafenozide	4	1			1	1			1		
Clethodim	9		3		4				1	1	
Clodinafop-propargyl	4					2			1	1	
Clofentezine	14	2						6	5	1	
Clomazone	9		2		3		1	3			
Clopyralid	8		1	1	1			3	1	1	
Cyflufenamide	9	4			1	3			1		
Cyfluthrin	3		1		2						
Cyhalofop-butyl	1					1					
Cymoxanil	8	3	2	3							
Cypermethrin	5		2	1	1	1					
Cyproconazole	13	3	1		2	1		3	2	1	

Active substance name (trivial)	Sum of maps	Fruit	Root crops	Leafy crops	Pulses & oilseeds	Cereal/ Grass crops	Miscellaneous	Rotational crops	Ruminant	Poultry	Fish
Cyprodinil	16	4	2			2		6	1	1	
Deltamethrin	6	1		1	1	1			1	1	
Desmedipham	2		2								
Dichlobenil	2	2									
Dichlorprop-P	1					1					
Dichlorprop-P 2-Ethyl hexyl ester	1	1									
Difenoconazole	21	3			2	2		7	3	4	
Dimethenamid-P	8		1		1	1		3	1	1	
Dimethoate	5	1	1			1			1	1	
Dimethomorph	19	3	3	2				7	2	2	
Dimoxystrobin	7				2			3	1	1	
Dodine	4	2					1		1		
Epoxiconazole	18		1			4	2	7	3	1	
Ethametsulfuron	1				1						
Ethephon	4	1			1	1				1	
Ethofumesate	15		3			1		7	2	2	
Etoxazole	10	5			2			3			
Famoxadone	6		1		1	1		3			
Fenhexamid	4	1		1	1				1		
Fenoxycarb	6	3				1			1	1	
Fenpropidin	15	2	1			3		6	1	2	
Fenpyroximate	14	6		1	1			6			
Flazasulfuron	3	2					1				
Florasulam	3					1			1	1	

Active substance name (trivial)	Sum of maps	Fruit	Root crops	Leafy crops	Pulses & oilseeds	Cereal/ Grass crops	Miscellaneous	Rotational crops	Ruminant	Poultry	Fish
Florpyrauxifen-benzyl	6					1		3	1	1	
Fluazifop-p	7		3	1	1				1	1	
Fluazinam	8	2	2		1			3			
Fludioxonil	20	4	1	2	1	1		9	1	1	
Flufenacet	22		2		2	4		9	2	2	1
Fluopicolide	4	1	1	1						1	
Fluopyram	18	4	2		2			6	2	2	
Fluoxastrobin	20	2			3	4		9		2	
Flupyradifurone	21	5	2		2	2		6	2	2	
Fluquinconazole	1								1		
Flutianil	4	3		1							
Flutolanil	16		2	1	1	2		6	2	2	
Flutriafol	15		1		1	1		10	1	1	
FOE Oxalate (Flufenacet met.)	2								1	1	
Folpet	6	2	1			1			1	1	
Forchlorfenuron	1	1									
Glyphosate	23	3	1		6	3		6	2	2	
Hexythiazox	11	5					1	3	1	1	
Indoxacarb	5	2			1				1	1	
IN-SXS67	1								1		
Iodosulfuron	4					2			1	1	
Ipconazole	7				1	2		3	1		
Iprodione	2		1							1	
Iprovalicarb	7	2	1					3	1		
Isofetamid	11	1		1	1			6	1	1	

Active substance name (trivial)	Sum of maps	Fruit	Root crops	Leafy crops	Pulses & oilseeds	Cereal/ Grass crops	Miscellaneous	Rotational crops	Ruminant	Poultry	Fish
Isoflucypram	21	2	2		4	2		6	2	2	1
Isopyrazam	7	1		1		1		3	1		
Isoxaben	4				1	3					
Isoxaflutole	10				2	4	1	3			
Lenacil	4		1					3			
Maleic hydrazide	3		3								
Mandestrobin	5			1	1			3			
Mefentrifluconazole (BAS 750F)	9	1			1	1		3	1	1	1
Mepanipyrim	7	4						3			
Mepiquat-chloride	6				2	1		3			
Mesosulfuron (-methyl)	2					2					
Mesotrione	6				3	2		1			
Metconazole	10	2			3	2			2	1	
Methoxyfenozide	9	2		1	1			3	1	1	
Metiram	8	1	1	1				3	1	1	
Metrafenone	1					1					
Metribuzin	10	2			1	2		3	1	1	
Metsulfuron-methyl	3				1				1	1	
Milbemectin	3	3									
Myclobutanil	8	3	1			2			1	1	
Napropamide	10	2	1	1	1			3	1	1	
Oxathiapiprolin	8	1	1	1				3	1	1	
Paclobutrazol	4				1			3			
Penconazole	3	3									

Active substance name (trivial)	Sum of maps	Fruit	Root crops	Leafy crops	Pulses & oilseeds	Cereal/ Grass crops	Miscellaneous	Rotational crops	Ruminant	Poultry	Fish
Pethoxamid	11		1		1	1		6	1	1	
Phosmet	6	2	1			1			1	1	
Picloram	10				1	1		6	1	1	
Pinoxaden	6					3		3			
Prochloraz	5	1	1			1	1		1		
Propamocarb	7	2	1	2					1	1	
Propoxycarbazone (sodium)	8					1		3	2	2	
Propyzamide	9		1	1	2			3	1	1	
Prosulfuron	6					2			2	2	
Prothioconazole	17		2		2	4		6	1	2	
Prothioconazole (-desthio)	2								2		
Pymetrozine	24	3	3		2	4		8	2	2	
Pyraclostrobin	15	1	1	1		3		6	1	1	1
Pyraflufen-ethyl	9	1	1		1	1		3	1	1	
Pyrimethanil	12	3	1	2		1		3	1	1	
Quinmerac	7		1		1	1		3		1	
Silthiofam	4					1		3			
Sintofen	3					2			1		
S-metolachlor	12		1		2	3		4	1	1	
Sodium Trifluoroacetic acid (TFA) (Flufenacet met.)	2								1	1	
Spiroxamine	16	3				2		9	1	1	
Sulfosulfuron	4					1		3			
Sulfoxaflor	9	1		1	1	1		3	1	1	
tau-Fluvalinate	10	1			4	3			2		

Active substance name (trivial)	Sum of maps	Fruit	Root crops	Leafy crops	Pulses & oilseeds	Cereal/ Grass crops	Miscellaneous	Rotational crops	Ruminant	Poultry	Fish
Tebuconazole	21	2			3	5		6	2	3	
Tembotrione	7				2	2		3			
Tetraconazole	14	2	2			2		6	2		
Thiabendazole	3	1							1	1	
Thiacloprid	9	2	1		2	4					
Thiadone-N-Glycoside	1								1		
Thifensulfuron (-methyl)	9				2	5			1	1	
Tolclofos-methyl	5		2	1					1	1	
Tolpyralate	6					1		3	1	1	
Topramezone	5					1		2	1	1	
Triadimenol	11	1	1			1		6	1	1	
Triallate	3				1	2					
Tribenuron-methyl (DPX-L5300)	12	1			2	4		3	1	1	
Trifloxystrobin	23	4	2		1	4		8	2	2	
Triflusulfuron.methyl	9		1					6	2		
Trinexapac-ethyl	11				2	3		3	1	2	
Triticonazole	5					4			1		
Tritosulfuron	8					2		4	1	1	
X11719474 (Sulfoxaflor met.)	2								1	1	
Zoxamide	10	4	1		1			3	1		

4. Conclusions

The deliverables of the project are considered as adequately and timely submitted within the agreed timeline of 15 June 2022. All xml-files have been coded according to agreed principles, and the 1265 submitted maps are within the agreed range of 1200 to 1350 maps (94% achievement rate).

5. Recommendations

5.1. Completion of the data base

According to the tender specifications, the number of created metabolism pathway maps envisaged by this project is approximately 1200 to 1350. At the end of the project phase, 40 studies (similar to ca 50 maps) out of the list of provided studies by EFSA remain open for coding.

It is recommended that these studies will be coded in order to complete the data base for the envisaged active substances under the current project.

5.2. Dealing with inconsistencies within the project and legacy data base

It is noted that for different reasons the MetaPath data base on regulatory metabolism studies exhibits some inconsistencies, which derived from changing coding practices since beginning of the MetaPath development in 2005.

First, the version history of Metapath and MSS Composer software evolved before and during the project, usually upon recommendations of EFSA project partners, OECD MUG Members, or other contractors: Bugs were fixed, new coding, displaying, searching and exporting functionalities were included, structure editors developed, coding flexibilities added by removal of cell restrictions, and many more. This refers for instance to the additional EFSA specific identifiers for chemical substances (PARAM code), extraction of analytical results for further processing in a separate spreadsheet, or coding of generic structures in Appendix 2 of MSS Composers or MetaPath.

As a consequence, EFSAs substance identifiers (PARAM codes) are missing for 543 studies or amendments, which have been submitted from 31 January 2020 (first submission) until 04 April 2021. They code for in total 583 maps and refer to the 71 active substances and/or their metabolites in Table 2.

Table 2: Active substances and metabolites, for which no PARAM-Codes have been attributed to the respective xml-files (all MSS Composers)

1,3 dichloropropene	Cyproconazole	Mepiquat-chloride
1,4-dimethylnaphtalene	Dichlorprop-P	Metconazole
2,4 DB	Dichlorprop-P 2-Ethyl hexyl ester	Metrafenone
6-Benzyladenine	Difenoconazole	Myclobutanil
Abamectin	Dimoxystrobin	Paclobutrazol

Acequinocyl	Dodine	Penconazole
Acetamiprid	Epoxiconazole	Phosmet
Alpha-cypermethrin	Ethephon	Propamocarb
Ametoctradin	Tebuconazole	Prosulfuron
Amidosulfuron	Tembotrione	Prothioconazole
Amisulbrom	Tetraconazole	Prothioconazole (-desthio)
Asulam	Fludioxonil	Pyraclostrobin
Benalaxyl	Fluoxastrobin	Pyrimethanil
Benthiavalicarb	Fluquinconazole	Quinmerac
Bixafen	Flutianil	Sintofen
Boscalid	Flutolanil	S-metolachlor
Bromuconazole	Flutriafol	Thiacloprid
Captan	Folpet	Tolclofos-methyl
Chlorothalonil	Hexythiazox	Tolpyralate
Chlorpropham	Ipconazole	Triadimenol
Chromafenozide	Isofetamid	Triallate
Clofentezine	Isopyrazam	Trifloxystrobin
Clomazone	Isoxaben	Triflusulfuron-methyl
Clopyralid	Lenacil	Triticonazole
Cyflufenamide	Mefentrifluconazole (BAS 750F)	Tritosulfuron

Additional reference specific identifiers (U.S. EPA MRID, CAN PMRA code, BfR eASB number) are also incompletely introduced to the data base.

Second, no full harmonisation in terminology was achieved due to missing pick-lists and fully manual data extraction and input - neither within the project groups (BfR, ANSES) or across the groups, nor across the full history of data base development (legacy data and EFSA collection of maps). For example, in the combined legacy and EFSA data base of the first 1398 maps, 12 different expressions exist for `apple´ as a test crop in plant metabolism studies (see Figure 2). Similar inaccuracies are found for other crops, animals (DER and MSS composers), and rotational crops. It is not clear, how many files are affected.

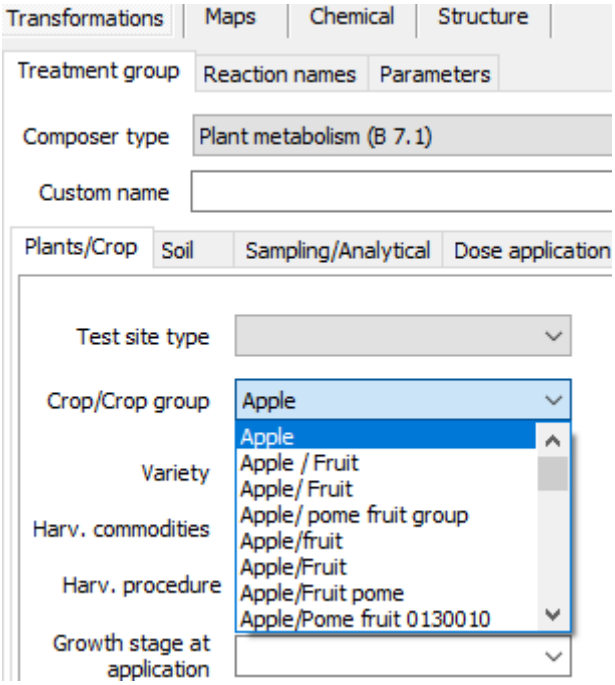


Figure 3: Examples of different expressions of Crop/Crop group in the combined Legacy/EFSA data base.

Equally relevant may be cases, where the type of identifier has different expressions: ´EFSA: PARAM`/ `PARAM code`exist in parallel, and so do ´US EPA: PC code`/´PC code`/´PC` (Fig. 3). Although attempts were made to harmonise the data input across the project staff, inconsistencies still passed internal and external validation processes. It is not clear, how many files are affected.

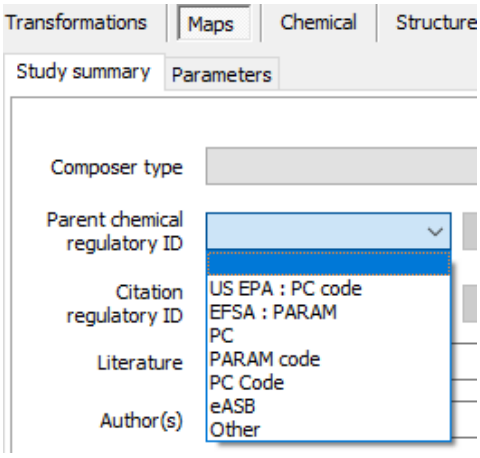


Figure 4: Examples of different expressions of Citation regulatory identifiers in the combined Legacy/EFSA data base.

It is also noted, that study reports often differ in their reporting practice of non-detects; these may be reported as "N/A", "-" , "<LOD" or simply as empty cell. While a full harmonisation of

coding throughout all maps would be desireable and would help to avoid ambiguities, this goal has not been achieved in the project due to the expected high workload and little gain.

Third, all partners (EFSA, BfR, ANSES) agreed in course of the project that additional study information on soil analyses may be relevant for profound later evaluations of metabolism studies: This refers mainly to rotational crop, but (occasionally) also to plant metabolism studies. This was not seen as mandatory at the beginning of the project, but was included on a voluntary basis in the coding practice during OF 3. BfR has access to 127 rotational crop metabolism studies in house, in which soil residue data (TRR, partly extractabilities and identified residues) have been reported.

Not only changing coding practices may hinder an effective search strategy of evaluators using MetaPath. Also the notional incompleteness of principally available analytical study results on soil metabolites interferes with efficient evaluation practice.

In order to reduce the impact of inconsistencies in studies coded within the project, it is recommended

1. To re-open all xml-files of rotational crop metabolism studies coded during the project and include missing soil degradation data, if available. Suggested priority: High.

   Justification: Soil residue data play a key role in the evaluation of potential uptake of soil residues by crops and transfer to feed and/or food commodities. Like for plants, overlaps of degradation pathways exist in soil for some substances of similar chemical classes. For example, the degradation of pyrazole-carboxamide to pyrazole acid and desmethyl pyrazole acid is described for the active substances isopyrazam, benzovindiflupyr, fluxapyroxad, bixafen, sedaxane and pydiflumethofen.

2. To re-open all xml-files coded during the project to include missing PARAM codes; this refers to all studies coded before April 2021. Suggested priority: Medium.

   Justification: It was considered by EFSA as of high importance to include the PARAM code to each xml file. While this could be done for consistency reasons, it is to be noted that the legacy data base does not consider PARAM codes, and therefore the search in MetaPath for a PARAM code only refers to a subset of the data base (see point 5.3. below).

3. To re-open all xml-files coded during the project and harmonise entries in Crop/Crop group and Livestock. Suggested priority: Low.

   Justification: It is considered that harmonisation of entries does not have a significant impact on the results of search queries and that efforts for harmonisation are disproportionate to the added value for risk assessors. Experienced users of MetaPath will be able to formulate appropriate search strings, where non-harmonised entries do not have an impact on the results.

5.3. Implementation of generic chemical structures in the data base

A very valuable tool has been included by the program developer LMC Burgas at a late stage of the project (v.1.10, March 2022): The option for coding and searching generic chemical structures. This feature has not been considered in the execution of the project tasks for maintaining consistency of the data base as much as possible (>1150 maps already submitted at release).

However, it is recommended, that the use of this feature is made mandatory as soon as the xml files from the legacy data base and EFSA´s collection of maps will be re-opened for whatever reasons, and that all chemical structures, which are coded as proxies to generic chemical structures will be transferred to an exact representation of the reported generic structure.

5.4. Open up data base for re-working

Experience has shown that inconsistencies across the study files (additional to those mentioned in 5.2) are likely to be detected during future evaluation work. The same applies to yet undetected coding errors or, equally important, incompletenesses in terms of a lack of desireable, but principally available information or data like soil residue characterisation and identification works.

Moreover, the project aimed to extract and collate only the most relevant information out of the metabolism study reports, while additional informations like on study set-up, physico-chemical properties, analytical methods or environmental conditions have been only coded to an agreed minimum level.

It should be also considered that, depending on the intended use of the data base informations (e.g. reporting the studies for regulatory purposes, research work on metabolic predictions or effectiveness of analytical extraction methods), data enrichment of the files with further study details may be required.

As a last point, developments of the MetaPath software package and/or availability of external metabolism data bases from third parties require constant examinations and re-working of data files to maintain the additional value of this evaluation tool could be necessary.

It is therefore recommended to open-up the files for a constant review and update and to develop a governance scheme that allows – inter alia – re-working of the existing files.

5.5. Update of U.S. PC Codes and EFSA´s PARAM codes

The U.S. EPA´s unique substance identifiers (Pesticide Chemical Codes or PC Codes) have been included in the entire data base of legacy data as well as EFSAs collection of maps. This is a unique feature in the data base, which is not shared by any other identifier. PC codes are therefore principally a suitable element for search queries. However, PC codes are not attributed to all active substances yet, so that for 66 studies coded within the project no PC numbers have been included. These studies code for 66 maps and refer to 9 active substances or their metabolites.

Table 3: Active substances and metabolites, for which no U.S. PC Codes have been attributed to the respective xml-files (all MSS Composers)

Amidosulfuron	FOE Oxalate (Flufenacet metabolite)	Picolinafen
Dichlorprop-P 2-Ethyl hexyl ester	Maleic hydrazid	Sintofen
Dimoxystrobin	Isoflucypram	Tritosulfuron

It is recommended to include the PC codes of the substances in Table 2 in EFSAs collection of maps as soon as these codes become available.

In addition, it might be considered by EFSA to update the legacy data base by PARAM and PC codes.

5.6. Lessons learned

Although the project was well planned in advance, the tasks and responsabilities appropriately attributed to and executed by the project partners, and the procedures in coding, filing and communication continuously amended to the needs in a timely manner, we still see some potential for improvements for similar projects in the future. This refers to two points, which are linked to the selection and exchange of studies for coding:

a) **Selection of studies**: EFSA assigned batches of studies for coding to the contractor at various time-points throughout the project. These studies were identified by EFSA as part of its responsabilities. The criteria for selection were set by EFSA, while the contractor was given the opportunity for study proposal and commenting. EFSAs selected criteria, although not specified in a written form, were mainly of formal nature like GLP status, active substance approval, extent and actuality of EU evaluation, etc. This is considered appropriate since the study packages are very large and cover a wide range of substance chemical classes and consequently also toxicological as well as residue properties of pesticides. However, if in the future additional smaller study packages are to be included in the data base, we recommend that the regulatory needs and available pre-informations are more put into the focus, like: Which chemical substance classes in the data base are already covered by large data sets, which not? Do the documented properties of candidate substances (toxicological, residues, environmental fate) allow a ranking for inclusion into the data base? The targeted selection of studies might also consider upcoming regulatory tasks like fertiliser additive evaluations, recent developments of classical endpoint assessments (e.g. information demands for the assessment of soil residue uptake by rotational crops), or extension of MetaPath to other regulated areas. The selection of studies of lower quality (e.g. non-GLP, incomplete reporting, literature data, qualitative or semi-quantitative analysis) could also be considered to close knowledge gaps in the data base for less covered chemicals.
b) **Format of study lists**: Studies for coding were forwarded from EFSA to the contractor in a non-standardised way by separate text tables in word format, pdf-files, or by email. It is recommended that study lists in future projects will be exchanged as one expandable file via excel or similar.

References

None.

Glossary

Metabolic map	A metabolic map is considered as an individual metabolic pathway, which is generated in one residue metabolism study and which covers one applied treatment regime. Different application rates or the use of active substances radiolabelled at different positions will be regarded as one metabolic map, if the data are generated within one metabolism study. However, where different crops or species are investigated within one metabolism study (e.g. rotational crop studies involving three or four different crops), or where soil and foliar treatment have been investigated in separate trials, the metabolism in each crop or species or treatment regime is considered as a separate metabolic map.

Annex A – Minimum information requirements for coding plant, rotational crop, and livestock metabolism studies in MSS Composers (taken from Annex 3 of EFSA Tender Specifications)

X: fields with information considered necessary to fill in
uncrossed : information that would not be considered as essential to fill in.

B.7.1 Metabolism, distribution and expression of residues in plants (Annex IIA 6.2.1) and
B.7.9 Metabolism in succeeding crops (Confined Accumulation in RC; Annex IIA 6.6)

	Tender
I. GENERAL INFORMATION	
Reference	
Author	**X**
Date	**X**
Study title	**X**
Pages	
Reference type	**X**
Testing laboratory	**X**
Company study number	**X**
MRID Number	
PMRA Number	
Other Identifier	**X**
Test Material	**X**
PC code	**X**
Guidelines	**X**
GLP	**X**
Acceptability	**X**
Background information *(free text)*	
Evaluator	**X**
Evaluator affiliation	**X**
Product type	
Product use	
Executive summary *(free text)*	
II. MATERIALS AND METHODS	
A. MATERIALS	
1. Test Material	
Common name	**X**
CAS Chemical Name	**X**

	Tender
CAS no.	X
Company experimental name	X
Other synonyms (if applicable)	
Molecular Formula	X
Analytical Purity	
Impurities	
Physical State	
Stability Under Test Conditions	
Expiration Date	
Lot/Batch #	
Radiolabeled test material	
Radiochemical purity	X
Specific activity as received:	
Specific activity of dose:	X
Structure	X
Physicochemical Properties	
Melting point/range	
pH	
Density	
Water solubility (__°C)	
Solvent solubility (mg/L at __°C)	
Vapour pressure at __°C	
Dissociation constant (pKa)	
Octanol/water partition coefficient Log(Kow)	X
UV/visible absorption spectrum	
2. Test Crops	
Crop/Crop Group	X
Variety	X
Growth Stage at Application	X
Growth Stage at Harvest	X
Harvested Commodities	X
Harvesting Procedure	
Test site type	
3. Soil Type	
Soil Type	X
pH	
OM %	
Sand %	
Silt %	

	Tender
Clay %	
Moisture Holding Capacity (at 1/3 bar)	
CEC mg/100g	
Environmental conditions	
Temperature	
Rainfall	
Lighting	
Potential for degradation of the substance	
B. STUDY DESIGN	
Experimental conditions *(free text)*	
Use pattern information	
Chemical name	
Application method	**X**
Application rate	**X**
Number of applications	**X**
Timing of applications	**X**
PHI	**X**
Sampling *(free text)*	**X**
Extraction and analysis *(flowcharts)*	
Extraction and Analysis *(free text)*	**X**
Identification and Characterization *(free text)*	**X**
III. RESULTS AND DISCUSSION	
A. TOTAL RADIOACTIVE RESIDUES	
Recovered equivalents	
Overall extraction efficiency	
Defined residue	
Defined residue extraction efficiency	
Quantitation *(free text)*	
TRR in matrices	
Matrix	**X**
Timing and application	**X**
Preharvest Interval (days)	**X**
% TRR	**X**
ppm	**X**
B. EXTRACTION, CHARACTERIZATION, AND DISTRIBUTION OF RESIDUES	
Distribution of the parent and Metabolites in Plant Matrices	**X**
C. STORAGE STABILITY OF RESIDUES	
Summary of storage conditions	

	Tender
D. IDENTITY OF RESIDUES IN RUMINANT	
Summary of characterization and identification of radioactive residues in plant matrices	**X**
E. PROPOSED METABOLIC PATHWAY	**X**
IV. CONCLUSIONS	
Conclusion *(free text)*	
References *(free text)*	
V. APPENDIX	
Appendix 1	
Test#	**X**
Number	
Application Method	**X**
Number of Applications	**X**
PHI	**X**
Matrix	**X**
Experimental descriptor	
Remarks	
Citation	**X**
RLMT	**X**
Test crop	**X**
Soil type	**X**
Appendix 2	
ID	**X**
Common name/Code	**X**
Chemical name	**X**
SMILES	**X**
Parent(s)	**X**
Expertise	**X**
Appendix 3	**X**
VI. ATTACHMENTS	

B.7.2 Metabolism, distribution and expression of residues in livestock (Annex IIA 6.2)

	Tender
I. GENERAL INFORMATION	
Reference	
Author	**X**
Date	**X**

	Tender
Study title	X
Pages	
Reference type	X
Testing laboratory	X
Company study number	X
MRID Number	
PMRA Number	
Other Identifier	X
Test Material	X
PC code	X
Guidelines	X
GLP	X
Acceptability	X
Evaluator	X
Evaluator affiliation	X
Background information *(free text)*	
Executive summary *(free text)*	
II. MATERIALS AND METHODS	
A. MATERIALS	
1. Test Material	
Common name	X
CAS Chemical Name	X
CAS no.	X
Company experimental name	X
Other synonyms (if applicable)	
Molecular Formula	X
Analytical Purity	
Impurities	
Physical State	
Stability Under Test Conditions	
Expiration Date	
Lot/Batch #	
Radiolabeled test material	
Radiochemical purity	X
Specific activity as received:	
Specific activity of dose:	X
Structure	X
Physicochemical Properties	
Melting point/range	
pH	

	Tender
Density	
Water solubility (__°C)	
Solvent solubility (mg/L at __°C)	
Vapour pressure at __°C	
Dissociation constant (pKa)	
Octanol/water partition coefficient Log(Kow)	**X**
UV/visible absorption spectrum	
2. Animals	
Species	**X**
Breed	**X**
Age	**X**
Weight at Study Initiation (kg)	**X**
Health Status	**X**
Description of Housing/Holding Area	**X**
B. STUDY DESIGN	
Dose regime	
Composition of Diet	**X**
Feed consumption (kg/day)	**X**
Water	
Acclimation period	**X**
Predosing	
Treatment type	**X**
Treatment level	**X**
Vehicle	
Parameters	
Dosage Rate	**X**
Timing/duration	**X**
Timing from final dose to sacrifice	**X**
Number of Animals per dose group	**X**
Rationale for selection of dose group	
Analysis of feed and water	
Sampling	
Milk collected	**X**
Amount of milk produced during normal production	
Urine, feces and cage wash collected	
Interval from last dose to sacrifice	
Tissues, harvested and analysed	**X**
Extraction and Analysis *(free text)*	**X**
Extraction and Analysis *(flowcharts)*	

	Tender
Identification and Characterization *(free text)*	**X**
III. RESULTS AND DISCUSSION	
A. TOTAL RADIOACTIVE RESIDUES	
Recovered equivalents	
Overall extraction efficiency	
Defined residue	
Defined residue extraction efficiency	
Quantitation *(free text)*	
TRR in milk, tissue and excreta	
Matrix	**X**
% aministered zone	**X**
ppm	**X**
TRR in milk as function of time	
Interval	**X**
ppb	**X**
% of dose	**X**
Plateauing	**X**
General Health of animals	
B. EXTRACTION, CHARACTERIZATION, AND DISTRIBUTION OF RESIDUES	
Distribution of the parent and Metabolites in Ruminant Matrices	**X**
C. STORAGE STABILITY OF RESIDUES	
Summary of storage conditions	
D. IDENTITY OF RESIDUES IN POULTRY/LACTATING RUMINANTS/ OTHER ANIMALS	**X**
Summary of characterization and identification of radioactive residues in plant matrices	
E. PROPOSED METABOLIC PATHWAY	**X**
IV. CONCLUSIONS	
Conclusion *(free text)*	
References *(free text)*	
V. APPENDIX	
Appendix 1	
Test#	**X**
Sex	**X**
Number	**X**
Dose Route	**X**
Dose (nominal)	

	Tender
Dose (measured)	X
Dose Type	X
Test duration	X
Matrix	X
Experimental descriptor	
Remarks	
Citation	X
RLTM	X
Species	X
Diet	X
Dosing	X
Samples	X
Appendix 2	
ID	X
Common name/Code	X
Chemical name	X
SMILES	X
Parent(s)	X
Expertise	X
Appendix 3	X
VI. ATTACHMENTS	