Annex IV

Mapping the practices of scientific (risk assessment) evaluation of active substances used in plant protection products

Research paper
by Dr. Dovilė Rimkutė

Abstract

The regulation of risks and hazards is highly differentiated and contested within the EU and beyond, i.e. risk assessors arrive at different scientific conclusions. This study, first, maps the practices of scientific (assessments) of active substances used in plant protection products: glyphosate, 2,4-D, bentazone and neonicotinoid pesticides. Second, the study aims to explain 'why scientific divergences have emerged' and whether the scientific differences between different risk assessors can be explained by differences in their institutional designs (mandates, procedures, formal working policies) and/or the technical/scientific quality standards followed in the risk assessment processes. To that end, this study draws on the analysis of primary documents, semi-structured interviews with the representatives of agencies, as well as an online stakeholders' survey.

The study has shown that several factors have contributed to the explanation relating to the main research question of this research paper: 'Why do risk assessors arrive at different conclusions?' The results from desk research and semi-structured interviews suggest that the diverging scientific conclusions on the studied substances have emerged because different risk assessors have engaged in different types of scientific evaluations (hazard identification versus risk assessment), which is an important explanatory factor explaining discrepancies in scientific conclusions. Furthermore, the following factors were identified as important causes explaining scientific divergences in scientific evaluations: agencies relied on different data sources to assess risks and hazards; they applied different scientific approaches (i.e., methodologies) to assess the collected data; they engaged in the different interpretations when weighing indefinite results.

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Executive summary

Scientific risk assessments are devised to offer an analytical tool to assess scientific knowledge regarding potential hazards and risks to humans and the environment. The duties of regulatory agencies and bodies assigned with the hazard identification/risk assessment tasks are deemed to be a highly scientific activity, mainly entrenched in the technical use of scientific knowledge and technical data. However, the regulation of risks and hazards is highly differentiated and contested within the EU and beyond, i.e. risk assessors arrive at different scientific conclusions. This study contributes to the debate by, first, mapping the practices of scientific (risk assessment) evaluations of active substances used in plant protection products. Second, the study aims to explain 'why scientific divergences have emerged' and whether the scientific differences between different risk assessors can be explained by differences in (1) their institutional designs (mandates, procedures, formal working policies) and/or (2) the technical/scientific quality standards followed in the risk assessment processes. To that end, this study draws on the analysis of primary documents and publicly available information, semi-structured interviews with the representatives of (regulatory) agencies, as well as an online stakeholders' survey to study the scientific/technical, procedural, performative and ethical aspects of the European Food Safety Authority's (EFSA) work across a wide range of stakeholders and organisations (research community, national regulatory authorities, NGOs, industry, etc.).

This research paper has focussed on the following active substances: glyphosate (herbicide), 2,4-D (herbicide), bentazone (herbicide), neonicotinoids (insecticide). It has shown that the following scientific divergences have emerged between reputable risk assessors (for more information see Chapter 2):

- **Glyphosate:** The report released in 2015 by the International Agency for Research on Cancer (IARC), an agency linked with the World Health Organisation (WHO), classified glyphosate as 'probably carcinogenic to humans' (IARC, 2015). Other regulatory agencies and bodies reached the conclusion that glyphosate is unlikely to be genotoxic or to pose a carcinogenic threat to humans. Those regulators include: the German Federal Institute for Risk Assessment (BfR), the European Food Safety Agency (EFSA), the European Chemicals Agency (ECHA), the United States Environmental Protection Agency (US EPA), the New Zealand Ministry Environmental Protection Agency (NZ EPA), the Health Canada Department of National Public Health (PMRA), the Australian Pesticides and Veterinary Medicines Authority (APVMA) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR).
- **2,4-D:** The IARC has classified 2,4-D as 'possibly carcinogenic to humans', whereas other health and safety agencies worldwide and in the EU (including EFSA and the US EPA) do not currently consider 2,4-D to be a human carcinogen.
- **Neonicotinoids** (clothianidin, imidacloprid, thiamethoxam): EFSA reached the conclusion that the neonicotinoid pesticides cause an acute risk to bees (2013, 2018), while the American and Canadian regulatory authorities conclude that bees under fieldwork conditions are not exposed to the neonicotinoid pesticides to the extent which could cause an acute risk to them.

- **Bentazone:** Overall, agencies that have conducted hazard/risk assessments of bentazone agree on the core scientific conclusions regarding the risks caused by bentazone. National, EU-level and international risk assessors concluded that genotoxic, carcinogenic or neurotoxic effects are not produced by bentazone.

In Chapter 3, the study has assessed the institutional design of risk assessors and procedural mechanisms followed in the scientific assessments. The analysis has shown that different risk assessors possess different mandates which have different regulatory implications. The desk research and semi-structured interviews have indicated that the IARC is distinct from the risk assessors working in the regulatory context (e.g., BfR, EFSA, ECHA, US EPA). First, the IARC has a substantially different mandate and organisational mission. Second, the IARC and agencies working in the regulatory context have obligations to follow diverse procedures and rules in their scientific evaluation processes.

Chapter 4 has shown that several factors have contributed to the explanation relating to the main research question of this research paper: 'Why do risk assessors arrive at different conclusions?' The results from desk research and semi-structured interviews suggest that the diverging scientific conclusions on the studied substances have emerged because different risk assessors have engaged in different types of scientific evaluations (hazard identification *versus* risk assessment), which is an important explanatory factor explaining discrepancies in scientific conclusions. Furthermore, the following factors were identified as important causes explaining scientific divergences in scientific evaluations: (1) risk assessors relied on different data sources to assess hazards and risks and (2) they applied different scientific approaches (i.e., methodologies) to assess the collected data.

Finally, this research paper has drawn on an online stakeholders' survey to study the opinions of stakeholders about EFSA and its scientific risk assessments (see Chapter 5). The survey was filled in by 42 respondents, of which 55% were national competent authorities, industry/industry associations (15%), NGOs and advocacy groups (12%), research community (8%) and other groups. The survey results have shown that, overall, EFSA is a well-regarded organisation on various dimensions: technical/scientific, procedural, performative and ethical/moral. In particular, the scientific/technical aspects of EFSA's conduct are perceived positively by the stakeholders who have submitted their contributions to the survey. Furthermore, overall the respondents perceive EFSA as a credible regulatory body whose work is authoritative and free from the political influence. The survey indicated that overall EFSA is regarded as a transparent, trustworthy and independent organisation.

List of abbreviations

ACVM	Agricultural Compounds and Veterinary Medicines
ADI	Acceptable Daily Intake
AdoIs	Annual Declaration of Interests
AGRI	European Parliament's Committee on Agriculture and Rural Development
ANSES	French Agency for Food, Environmental and Occupational Health Safety
APVMA	Australian Pesticides and Veterinary Medicines Authority
ARfD	Acute Reference Dose
BASF	Baden Aniline and Soda Factory
BAuA	German Federal Institute for Occupational Safety and Health
BfR	German Federal Institute for Risk Assessment
BMEL	German Federal Ministry of Food and Agriculture
BMG	German Federal Ministry of Health
BMUB	German Federal Minister for Environment, Nature Conservation, Building and Nuclear Safety
BVL	German Federal Office of Consumer Protection and Food Safety
CAC	Codex Alimentarius Commission
CCPR	Codex Committee on Pesticide Residues
CLH	Harmonised Classification and Labelling
CLP	Classification, Labelling and Packaging
CMR	Carcinogenicity, Mutagenicity, Reproductive Toxicity
CoI	Conflicts of Interest
DFG	German Research Foundation
DG EPRS	Directorate General for Parliamentary Research Service
DGAL	French Directorate General for Food
DoI	Declaration of Interests
ECHA	European Chemicals Agency
ECPA	European Crop Protection Association
EFSA	European Food Safety Authority
ENVI	European Parliament's Committee on Environment, Public Health and Food Safety
EP	European Parliament
ESLC	Evidence suggests lack of carcinogenicity
EU	European Union
FAO	Food and Agriculture Organization
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FSCJ	Food Safety Commission of Japan
GAP	Good Agricultural Practice
GECU	Emergency Collective Expert Assessment Group
GHS	United Nations' Globally Harmonised System
GLP	Good Laboratory Practice
GM	Genetically Modified
GMO	Genetically Modified Organisms
HA	Health Advisory
HEAL	Health and Environment Alliance

HSNO	Hazardous Substances and New Organisms
IARC	International Agency for Research on Cancer
IESTI	International estimated short-term intake (IESTI)
INRA	French National Institute for Agricultural Research
IPCS	International Programme on Chemical Safety
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LOC	Maximum Level of Concern
LOEL	Lowest Observed Effect Level
MOE	Margin of Exposure
MPI	Ministry for Primary Industries
MRLs	Maximum Residue Levels
MSCA	Member State Competent Authority
NESTI	National Estimated Short-Term Intake
NOEC	No Observable Effect Concentration
NOEL	No Observed Effect Level
NRC	National Research Council
NTMDI	National Theoretical maximum daily intake
NZ EPA	New Zealand Ministry Environmental Protection Agency
OCSPP	EPA's Office of Chemical Safety and Pollution Prevention
ODoIs	Oral Declarations of Interest
OECD	Organization for Economic Cooperation and Development
OPP	Office of Pesticide Programs
PAN	Europe Pesticide Action Network Europe
PIC	Prior Informed Consent
PMRA	Health Canada Department of National Public Health
PPE	Personal Protective Equipment
PPP	Plant Protection Products
PPR	Panel on Plant Protection Products and their Residues
QMS	Quality Management System
RAC	Committee for Risk Assessment
RAR	Renewal Assessment Report
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
RED	Registration Eligibility Decision
RfD	Reference Dose
RIVM	National Institute for Public Health and the Environment
RMS	Rapporteur Member State
RQs	Risk Quotients
SAB	Science Advisory Board
SAP	Scientific Advisory Panel
SDoIs	Specific Declarations of Interest
SDWA	Safe Drinking Water Act
UN	United Nations
US EPA	United States Environmental Protection Agency
WG	Working Group
WHO	World Health Organisation
WoE	Weight of Evidence

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Chapter 1

I – Background

Scientific risk assessments are devised to offer an analytical means to assess scientific knowledge regarding potential hazards and risks to humans and the environment (Rimkutė, 2018). The duties of regulatory agencies assigned with risk assessment/hazard identification and classification tasks are deemed to be highly scientific activities, mainly entrenched in the technical use of scientific knowledge and technical data. However, the regulation of risks and hazards is highly differentiated and contested within the EU and beyond. Scholars analysing the practices of scientific risk assessments have observed that regulatory agencies' technical/scientific and procedural practices – i.e., the ways in which scientific knowledge is used in risk assessments – vary greatly (Bozzini, 2017; Peel 2010; Jasanoff 1995; Rothstein et al. 1999). The discussions between independent regulatory bodies become even more disputed when it comes to chemical, environmental or foodstuff policy-making (Lodge and Wegrich 2011; Lofstedt and Schlag 2016; Rimkutė 2015, 2016, 2018). For instance, independent regulatory agencies and bodies have taken a different scientific stance on pesticides, endocrine disruptors, air pollutants and genetically modified organisms.

More recently, heated debates emerged among national, EU and international regulators on different sides of the policy aisle on glyphosate where one group of risk assessors (working in non-regulatory environment) argues that the substance should be classified as 'probably carcinogenic' (the International Agency for Research on Cancer (IARC, 2017c)), while another group of risk assessors (working in regulatory environment) argues that glyphosate is "unlikely to pose carcinogenic hazard" (e.g., EFSA, 2015b; ECHA, 2017c; US EPA, 2016). Similar contradictions can be observed regarding other active substances: 2,4-D (herbicide); neonicotinoids (insecticide): clothianidin, imidacloprid, thiamethoxam.

Given these scientific controversies, this research paper aims to assess the scientific and procedural aspects of risk assessments that have led to regulatory controversies (i.e., a lack of scientific consistency among independent regulatory agencies and bodies). More specifically, this research paper, firstly, aims to map (regulatory) agencies and bodies that conducted scientific evaluations of five active substances: glyphosate; 2,4-D; bentazone; neonicotinoid pesticides (more specifically, clothianidin, imidacloprid, thiamethoxam). It briefly introduces the scientific conclusions reached and outlines the core disagreements between risk assessors. Second, this research paper aims to explain why scientific disagreements in scientific evaluations have occurred. To that end, the paper reviews the institutional designs of key agencies that have produced scientific evaluations of the active substances of interest. Furthermore, the paper examines which technical, procedural and scientific methods the agencies used throughout the scientific assessments, as specified in the analytical framework of the paper.

II – Analytical Framework

In this research paper, the risk assessors that have produced contradicting risk assessments are compared against the following criteria:

1. **The institutional design of risk assessors and procedural mechanisms followed in the scientific assessments:**
   - Formal mandate and accountability mechanisms;
   - Independence and transparency policies;
   - Selection of scientific experts: requirements for scientific experts (e.g., conflict of interest statements);
   - Procedures followed in the risk/hazard assessments;
   - Internal/external control mechanisms: quality standards followed in the risk assessments.

2. **The technical/scientific aspects of risk assessments:**
   - Scientific (quality) standards: the type of evidence used in the risk assessment (e.g., industry research, academic articles), data collection methods, scientific approaches followed to evaluate the collected data (e.g. Weight of Evidence (WoE) approach).

III – Methodology: data collection methods and comparison strategy

This research paper follows the technical specifications for the assignment. As requested, the research paper maps the bodies (i.e., (regulatory) agencies and independent expertise centres) that have carried out scientific assessments of the following active substances: glyphosate; bentazone; 2,4-D; neonicotinoids: clothianidin, imidacloprid, thiamethoxam. These substances were selected based on the controversies they have raised in terms of scientific assessments, and hence public concerns.

This research paper aims to map the most relevant national, EU-level and international bodies that have arrived at similar/different scientific conclusions (compared with the European Food Safety Authority (EFSA)) and review (1) the institutional design of risk assessors and procedural mechanisms followed in the scientific assessments, as well as (2) the scientific aspects of risk assessments. To that end, the research paper relies on the following information sources:

Primary documents: The study extensively relies on publicly available documents such as founding regulations, formal mandates, corporate documents (e.g., annual reports, policy and strategy documents). Publicly available documents on the procedural aspects of the risk assessments such as: minutes of working group meetings; documents specifying procedures followed; press releases of agencies and bodies. Publicly available documents on the scientific aspects of risk assessments were retrieved from the scientific outputs.

Semi-structured interviews: the study draws on semi-structured interviews with representatives of the examined (regulatory) agencies and bodies. Semi-structured interviews were conducted to obtain in-depth information about the technical and procedural aspects of risk assessors' scientific outputs. Interviews were structured around a set of broad topics and general questions reflecting the analytical framework of the research paper. [1]

The interviews were collected between the 7th of December 2017 and the 6th of April 2018 (see Annex I: List of interviews) with scientists and managers from the following authorities: the European Food Safety Authority (EFSA); the European Chemicals Agency (ECHA); the German Federal Institute for risk assessment (BfR); the Federal Office of Consumer Protection and Food Safety (BVL); the French Agency for Food, Environmental and Occupational Health & Safety (ANSES); the Australian Pesticides and Veterinary Medicines Authority (APVMA); and the US Environmental Protection Agency (US EPA) (written responses were provided). [2]

The list and names of relevant interviewees were accessed through the publicly available sources of information. The Ex-post Evaluation Unit of EPRS provided help in establishing contact with the interviewees from national and EU agencies. The author emphasised that the participation in the interview programme is entirely voluntary: interviewees had the right to refuse to participate or to withdraw their participation without any consequences. All relevant information about the research and interview procedures were introduced before the interview started.

The researcher made sure that the research does not lead (either directly or indirectly) to a breach of agreed confidentiality and anonymity. No individual information and other personally identifiable information is used in the research paper (unless the interviewees noted that their personal names can be revealed). To maintain the anonymity of the interviewees' personal information, only partial information is provided, e.g. *Agency representative #1.*

The researcher asked permission to record the interview. If consent was given, the interviews were audio-recorded and transcribed. The interviewees were also able to choose not to be audio-recorded, in which case the researcher took notes and summarised what the interviewees communicated.

Stakeholder Survey: In addition to the desk research and semi-structured interviews, an online stakeholders' survey (entitled 'Study on the European Food Safety Authority and its risk assessment practices') was carried out from the 4th of January to the 23rd of February 2018 to collect opinions about the scientific risk assessment model established in the EU by Regulation (EC) 1107/2009 concerning the placing of plant protection products on the market. The questions explored the scientific, technical and procedural aspects of

[1] The list of interview questions could be submitted upon request.

[2] It is of note that IARC and PMRA (Canada) were available to give an interview and/or submit a written contribution but after the closure of data collection (6 April).

European Food Safety Authority's (EFSA) work across a wide range of stakeholders and organisations (research community, national regulatory authorities, NGOs, industry, etc.). The survey was disseminated to 293 stakeholders, including national competent authorities, PPP manufacturers and industry organisations, associations of PPP users, farmers' associations, (human and animal) health and environment NGOs, consumer groups, and research community (e.g., academics). The list of potential respondents was collected from EFSA's website, i.e. EFSA publishes a list of organisations and individuals who attend its events (stakeholder consultations, conferences, other activities organised by EFSA). The survey received 42 responses (response rate: 15%). For more information, see Chapter 5.

Data analysis: the analytical framework (outlined in II – Analytical Framework) was used to assess the technical and procedural aspects of the contradicting risk assessments, as well as the institutional designs of agencies and bodies that have produced them. The comparison is organised as follows:

1. **Comparisons across risk assessors in terms of their institutional designs:** At this stage of the research project, formal mandate and accountability mechanisms, independence and transparency policies; policies specifying the selection of scientific experts criteria, requirements for scientific experts, procedures followed in the risk/hazard assessments, and internal/external control mechanisms are introduced and compared across the selected sample of agencies. The following agencies were covered in the analysis: (1) Relevant EU agencies (the European Food Safety Authority and the European Chemicals Agency) and national competent authorities (the German Federal Institute for Risk Assessment); (2) Most prominent international bodies (the International Agency for Research on Cancer); and (3) Agencies working outside the EU (the United States Environmental Protection Agency).
   The selection of the aforementioned agencies for an in-depth analysis was motivated by the following. First, relevant EU agencies (EFSA and ECHA) were included in the analysis as they played an important role by providing the European Commission (the risk manager for approval of substances at EU level) with their scientific evaluations of active substances. Corresponding national authorities were also included in the analysis (e.g. the German (BfR)) as they issued the Renewal Assessment Report (RAR) on glyphosate on which EU agencies based their peer-reviews of pesticides. Last but not least, the IARC was selected as a case of an international regulatory body, and the US EPA as an independent regulatory agency functioning outside the EU. Furthermore, the US EPA is regarded as a typical case of the most relevant agencies operating outside the EU (i.e., Australian and Canadian regulatory agencies have comparable institutional designs to the American regulatory agencies). For more information on the case selection strategy and analysis, see Chapter 3.

2. **Comparisons of technical and scientific aspects of agencies** that have produced contradicting risk assessments. The same sample of agencies (EFSA, ECHA, BfR, IARC, US EPA) is covered in the comparison of scientific (quality) standards followed by agencies.

The core focus of comparison is on the glyphosate case. This focus has been selected due to the public interest in the issue, however, the interviewed representatives of regulatory authorities (e.g., EFSA, ECHA, BfR) confirmed that the same (or comparable) scientific practices were applied in evaluating other active substances (2,4-D; neonicotinoid pesticides; bentazone).

Chapter 2

I - Mapping regulatory agencies and their scientific conclusions

This chapter maps the bodies which have carried out scientific risk assessments of active substances, such as glyphosate, 2,4-D, bentazone and neonicotinoids. It reviews the most relevant national, supranational and international bodies that have assessed hazards/risks of the five active substances. The intended contribution of the mapping is, first, to identify which regulators conducted scientific evaluations of the active substance of interest. Second, the chapter aims to briefly discuss the scientific conclusions reached by different regulatory bodies.

Key findings

- **Glyphosate:** The report released in 2015 by the IARC, an agency linked with the World Health Organisation (WHO), classified glyphosate as 'probably carcinogenic to humans' (IARC, 2015). Other regulatory agencies and bodies reached the conclusion that glyphosate is unlikely to be genotoxic or to pose a carcinogenic threat to humans. Those regulators include: the German Federal Institute for Risk Assessment (BfR), the European Food Safety Authority (EFSA), the European Chemicals Agency (ECHA), the United States Environmental Protection Agency (US EPA), the New Zealand Ministry Environmental Protection Agency (NZ EPA), the Health Canada Department of National Public Health (PMRA), the Australian Pesticides and Veterinary Medicines Authority (APVMA) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR).
- **2,4-D:** The IARC arrived at the conclusion that 2,4-D should be classified as 'possibly carcinogenic to humans', whereas other health and safety agencies (including EFSA and the US EPA) do not currently consider 2,4-D to be a human carcinogen.
- **Bentazone:** EFSA and other agencies concluded that genotoxic, carcinogenic or neurotoxic effects are not produced by bentazone. However, EFSA, together with other regulatory agencies (e.g., US EPA), have identified several data gaps (in the mammalian toxicology area, in potential endocrine disrupting properties, risks to consumers etc.) which did not allow the finalisation of the risk assessment of bentazone.
- **Neonicotinoids:** In 2013 and 2018, EFSA reached the conclusion that the neonicotinoid pesticides (clothianidin, imidacloprid, thiamethoxam) cause an acute risk to honey bees, while the US EPA (and Canadian regulatory authorities) claimed that honeybees are not exposed to the neonicotinoid pesticides to the extent which could cause an acute risk to them.

1. Glyphosate

Glyphosate is one of the most widely used active substances, both worldwide and in the EU. The substance was discovered to be an herbicide by a Monsanto chemist in 1970. In 1974, glyphosate was introduced to market by Monsanto under the trade name Roundup. Glyphosate-based pesticides are utilised as herbicides in agriculture, horticulture, viticulture, silviculture, as well as garden maintenance (including home use). The primary use of this herbicide is aimed at combatting weeds (especially annual broadleaf weeds, grasses and woody plants) that compete with cultivated crops. The extensive use and public deliberation regarding glyphosate have stimulated societal concerns as well as a scientific controversy on the toxicity of glyphosate (Faria, 2015) beyond the scientific debate (Blaylock, 2015; Tarazona el al., 2017).

In the last 40 years, glyphosate has been assessed for safety by a multiplicity of national and international authorities, including the US EPA (1993), Australia (1996; 2016), WHO (1994), and the EU (2002; EFSA, 2015a; ECHA, 2017a), invariably giving an authorisation to glyphosate with some warnings about conditions for safe use. However, the debate surrounding the use of glyphosate in the European Union (EU) and beyond was initially sparked by the International Agency for Research on Cancer (IARC). On the 20th of March 2015, IARC published its scientific risk assessment classifying glyphosate as "probably carcinogenic" (IARC, 2017c). In parallel, risk regulators working at national, EU and international levels have carried out risk assessments of glyphosate to evaluate the (new) scientific data. The re-assessments were mainly carried out because the licence for the use of glyphosate was due to expire (e.g., in the EU, the due date was on the 30th of June 2016).

Regulatory agencies that possess (were given) a mandate to evaluate the risks of glyphosate have issued their evaluations of the active substance. The risk/hazard assessments were published by the regulatory agencies and bodies, such as the German Federal Institute for Risk Assessment (BfR), the French Agency for Food, Environmental and Occupational Health & Safety (ANSES), the European Food Safety Agency (EFSA), the European Chemicals Agency (ECHA), the United States Environmental Protection Agency (US EPA), the New Zealand Environmental Protection Agency (NZ EPA), the Health Canada Department of National Public Health (PMRA), the Australian Pesticides and Veterinary Medicines Authority (APVMA), the Food Safety Commission of Japan (FSCJ), and the Joint FAO/ WHO Meeting on Pesticide Residues (JMPR).

The agencies have come to different conclusions regarding the carcinogenic properties of glyphosate (see Table 1). The IARC concluded that glyphosate is "probably carcinogenic to humans" (IARC, 2017c), whereas other regulatory bodies including EFSA and ECHA agreed on the conclusion that glyphosate is unlikely to pose any carcinogenic hazard/risk to humans (ECHA, 2017a; EFSA, 2015a). ANSES stated that there is insufficient and inadequate analysis to produce any meaningful conclusion on the effects of glyphosate (ANSES, 2016b).

Table 1. Agencies' stance on the effects of glyphosate on human health

Glyphosate probably carcinogenic	Additional research must be conducted	Glyphosate poses no cancerous risk in humans
IARC	ANSES	BfR EFSA ECHA US EPA NZ EPA APVMA PMRA JMPR

In the remainder, the section reviews the regulatory authorities that have recently conducted scientific risk assessments of glyphosate, introduces the conclusions reached, and specifies the core scientific divergences between the IARC and other regulatory agencies. Furthermore, the section briefly discusses which risks of the active substance glyphosate were assessed by regulatory body and what the relevant agencies concluded.

1.1 Agencies concluding that glyphosate poses a carcinogenic hazard

International Agency for Research on Cancer (IARC)

An important actor in producing risk assessments for substances such as glyphosate is the International Agency for Research on Cancer (IARC). The IARC is a specialist branch of the World Health Organization (WHO). More specifically, they tackle issues in regard to cancer amongst the human population. Because of this, the focal point of their research on active substances takes the form of carcinogenic properties. Additionally, the IARC compiles any available information in a meta-analysis and then judges whether or not the substance poses a carcinogenic risk. The IARC does not claim whether or not the substance will directly cause cancer or not, but assesses the hazard and suggests, on a scale, how much of a carcinogenic risk the substance poses.

Specifically, when classifying an agent as carcinogenic, the IARC's scientific procedure is based on a table (see the table below and *Figure 1* and) in which both animal and human evidence are considered. A substance will only be classified as 'carcinogenic' (i.e., Group 1)[3] if there is sufficient evidence of it causing cancer in animals *and* humans (for more information please see: IARC, 2006). A substance will be classified as 'probably carcinogenic' (Group 2A) if there is limited evidence of carcinogenicity in humans *but* sufficient evidence of carcinogenicity in animals. An agent will be classified as 'possibly carcinogenic' (Group 2B) if there is inadequate evidence of carcinogenicity in humans *but* sufficient evidence of carcinogenicity in animals. Findings that fall outside of these areas

[3] which is the highest level of certainty compared to 'probably carcinogenic' (Group 2A) and 'possibly carcinogenic' (Group 2B).

are considered to be "not classifiable as to its carcinogenicity to humans" (Group 3). Group 4 refers to cases in which evidence suggests lack of carcinogenicity (ESLC) in both human and experimental animal studies.

The IARC scientific evaluation result in the classification of environmental factors in 5 groups:
Group 1 - Carcinogenic to humans
Group 2A - Probably carcinogenic to humans
Group 2B - Possibly carcinogenic to humans
Group 3 - Not classifiable as to its carcinogenicity to humans
Group 4 - Probably not carcinogenic to humans

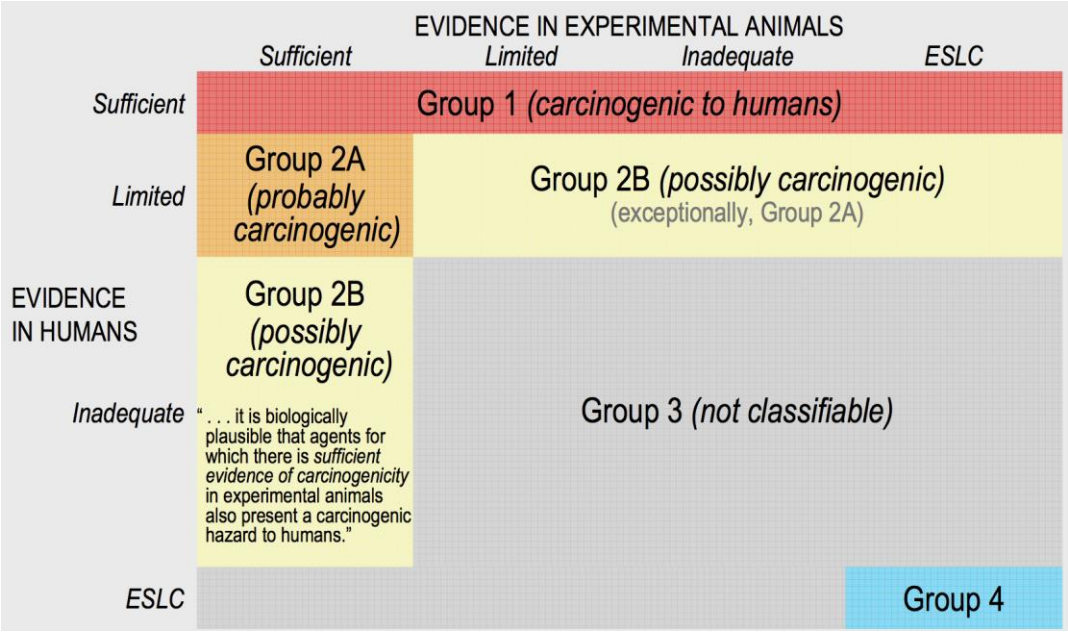

Figure 1. The logic behind the classification of environmental factors in 5 groups followed by the IARC

In the case of glyphosate, the IARC has undertaken extensive research and investigation on the impact that glyphosate has on human health. In 2014, an advisory group of 21 scientists from 13 countries and several government officials evaluated glyphosate. In March 2015, IARC classified glyphosate as 'probably carcinogenic to humans', placing it in Group 2A (IARC, 2017c).

The IARC has conducted a hazard-based and strength-of-evidence assessment of publicly available scientific information related to glyphosate. The study of the IARC scholars arrived at the conclusion for "limited" evidence of cancer in humans but "sufficient" evidence of cancer in animals. The IARC used case studies from the USA, Canada, and Sweden for their human evidence, whilst their animal evidence was derived from experiments conducted on laboratory animals (mice). Furthermore, the monograph concluded that glyphosate caused DNA and chromosomal damage in human cells and that

there was "strong" evidence for genotoxicity in chemical components like glyphosate (IARC, 2017c). See table below for more specific conclusions communicated by the IARC.

"There is strong evidence that glyphosate can operate through two key characteristics of known human carcinogens, and that these can be operative in humans. Specifically:

- There is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in humans in vitro and studies in experimental animals. One study in several communities in individuals exposed to glyphosate-based formulations also found chromosomal damage in blood cells; in this study, markers of chromosomal damage (micronucleus formation) were significantly greater after exposure than before exposure in the same individuals.
- There is strong evidence that glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid can act to induce oxidative stress based on studies in experimental animals, and in studies in humans in vitro. This mechanism has been challenged experimentally by administering antioxidants, which abrogated the effects of glyphosate on oxidative stress. Studies in aquatic species provide additional evidence for glyphosate-induced oxidative stress." (IARC, 2017c, p. 78-79)

One can observe that the IARC was one of the first bodies to warn about the possibility of glyphosate leading to cancer. However, the IARC classifications do not have regulatory implications. The IARC clearly states that they do not measure the likelihood that cancer will occur as a result of exposure (i.e., they do not provide a risk assessment, rather they provide hazard classification). In this way, the IARC avoids any legal ramifications in their pursuit of classifying herbicides as carcinogenic. However, the hazard classification of the IARC has influenced regulators, policy/decision-makers and the public. The scientific conclusions of the IARC have significantly shaped the glyphosate debate in Europe and worldwide. For instance, the regulatory agencies and bodies that assessed the risks of glyphosate to humans and the environment, also concentrated on evaluating and reflecting on the scientific output on glyphosate published by the IARC in 2015. The glyphosate peer review process of EFSA, for example, was delayed as the European Commission gave an additional mandate to EFSA to assess the scientific output of the IARC (EFSA, 2015a; EFSA representative #2).

1.2 Agencies concluding that glyphosate is unlikely to pose a carcinogenic risk/hazard

Joint FAO/WHO Meeting on Pesticide Residues (JMPR)

The Joint FAO/ WHO Meeting on Pesticide Residues (JMPR) is "an expert ad hoc body administered jointly by FAO and WHO" which has as its central mission "the purpose of harmonising the requirement and the risk assessment on the pesticide residues" (FAO, 2018). The JMPR has met annually since 1963 and continues to bring together multiple standpoints and scientific approaches of international scientists.

As in the case of the IARC, the JMPR only focussed on the carcinogenic properties of glyphosate. They explained this focus by stating: "There is a large body of literature regarding pesticide exposures and non-cancer outcomes (neurodevelopmental, neurodegenerative and reproductive outcomes, among other health outcomes), but the assessment of the epidemiological evidence on […] glyphosate [...] was restricted to studies of cancer outcomes. This restriction was partly driven by feasibility reasons: a clinically relevant adverse effect size (or an acceptable level of risk) for a non-cancer outcome must be defined, and the methodologies for hazard identification and [characterisation] based on observational epidemiological findings of non-carcinogenic adverse effects are less well established than those for cancer" (JMPR, 2016a, p. 4).

The WHO (through IARC) had already concluded that "glyphosate exposure could possibly lead to cancer" (IARC, 2017c). However, on the 9th–13th of May 2016, the JMPR, which gathered in Geneva, re-evaluated the risk assessment, which led to important conclusions. Regarding glyphosate specifically, the JMPR concluded that "glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet" (JMPR, 2016a, p. 2). More specifically, the JMPR concluded as follows: (see table below).

Summary Report from the May 2016 Joint FAO/WHO Meeting on Pesticide Residues (JMPR)

"The overall weight of evidence indicates that administration of glyphosate and its formulation products at doses as high as 2000 mg/kg body weight by the oral route, the route most relevant to human dietary exposure, ***was not associated with genotoxic effects in an overwhelming majority of studies conducted in mammals, a model considered to be appropriate for assessing genotoxic risks to humans***. The Meeting concluded that glyphosate is unlikely to be genotoxic at anticipated dietary exposures. […] The Meeting concluded that glyphosate is not carcinogenic in rats but could not exclude the possibility that it is carcinogenic in mice at very high doses. In view of the absence of carcinogenic potential in rodents at human-relevant doses and the absence of genotoxicity by the oral route in mammals, and considering the epidemiological evidence from occupational exposures, the ***Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet***. The Meeting reaffirmed the group ADI [Acceptable Daily Intake] for the sum of glyphosate and its metabolites of 0–1 mg/kg body weight on the basis of effects on the salivary gland. The Meeting concluded that it was not necessary to establish an ARfD [Acute Reference Dose] for glyphosate or its metabolites in view of its low acute toxicity." (JMPR, 2016b, p. 2)

A joint expert taskforce consisting of scientists from the World Health Organization (WHO), national authorities and universities pooled scientific capacities in May 2016 to review the information analysed by the IARC in order to evaluate and decide if there is a necessity to revise previous assessments on glyphosate undertaken by the Joint FAO/WHO Meeting on Pesticide Residues (or JMPR) in 2003, 2006 and 2011. The joint expert taskforce reached the conclusion that, while there was some evidence for a positive

association between occupational glyphosate exposure and non-Hodgkin lymphoma in several studies, the only reliable study (i.e., well-designed large cohort study) found no correlation at any exposure level (JMPR, 2016a). They concluded that the general weight-of-evidence suggests that glyphosate is not genotoxic in mammals. Furthermore, they indicated that, even at high doses, glyphosate is unlikely to be genotoxic to humans (at likely levels of dietary exposure). Finally, the JMPR arrived at the conclusion that glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet (WHO, 2016).

However, the JMPR only assessed the effects of glyphosate through dietary consumption, which poses certain limitations. Nevertheless, the JMPR does acknowledge that it is hard to extrapolate the results and the effects that glyphosate has on rodents to human beings (JMPR, 2016a). Based on these limitations, the JMPR has encouraged further risk assessments efforts as it understands the limitations the studies have.

The German Federal Institute for Risk Assessment (BfR)

In August 2014, glyphosate was re-evaluated by the Rapporteur Member State (RMS) Germany (the BfR in particular), as mandated by the European Commission and organised by the European Food Safety Authority (EFSA). In particular, the BfR made hazard identification and initial risk assessment of toxicology aspects (including carcinogenicity) of the substance. Please see the underlying procedure of the safety of pesticides assessments in the EU in the table below.

Under EU legislation (Regulation (EC) 1107/2009), pesticide active substances in plant protection products are approved in the EU only if it may be expected that their use will not have any harmful effects on human and animal health or the environment. The evaluation of both existing and new active substances follows a phased approach:

"For each substance an initial draft assessment report (DAR) or renewal assessment report (RAR) is produced by a rapporteur Member State (RMS). Regarding applications for renewal of an approval, the Commission decides on the designation of a rapporteur Member State in consultation with all Member States and industry.

The RMS's risk assessment is peer reviewed by EFSA in cooperation with all Member States and other stakeholders.

EFSA drafts a report ("Conclusion") on the active substance. The EFSA Conclusion informs the European Commission in the approval process, the subsequent assessments of plant protection products (that will contain this active substance) done by the Member States, and the revision of maximum residue levels in food by EFSA.

The European Commission decides whether or not to include the substance in the EU's list of approved active substances. This determines whether the substance can be used in a plant protection product in the EU.

EU Member States assess or re-assess the safety of plant protection products containing the active substance that are sold in their territory" (EFSA, 2015d, p. 3).

The German Federal Institute for Risk Assessment (BfR) concluded that glyphosate is "unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential" (EFSA, 2015g). They concentrated on the use of glyphosate as an herbicide on "emerged annual, perennial and biennial weeds" (EFSA, 2015g).The emphasis was put on the correct usage of the substance and no repetition of high dosages. Under these circumstances, glyphosate was evaluated by the BfR as safe for humans and animals and not being carcinogenic, leading to reproductive problems nor causing malformations.

The BfR's scientific evaluation of the dossier on glyphosate in the Renewal Assessment Report (RAR) was forwarded to EFSA on the 20th of December 2013. After receiving the comments on the RAR, it was decided that EFSA should conduct an expert consultation in the areas of mammalian toxicology, residues, environmental fate and behaviour and ecotoxicology. EFSA was asked by the Commission to adopt scientific conclusions on whether the active substance glyphosate can be expected to meet the conditions provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and the Council. To that end, on the 6th of August 2014, EFSA was mandated by the European Commission to provide the peer review of the active substance glyphosate (EFSA, 2015b, p. 2).

European Food Safety Authority (EFSA)

The assessment of glyphosate in the EU has taken three years, involving public sector scientific experts from EU agencies as well as national authorities in all 28 Member States (European Commission, 2016). The European Food Safety Authority (EFSA) has played an important role in the process.

In August 2014, EFSA received a mandate from the European Commission asking to conduct the peer review of the active substance glyphosate. In April 2015, EFSA received a second mandate from the European Commission asking to consider the most recent conclusions by the IARC (2017c) regarding the conceivable carcinogenicity of glyphosate or glyphosate-containing plant protection products according to Regulation (EC) No 1272/2008. To complete this additional task, EFSA asked the Commission for an extension of the overall deadline to the 30th of October 2015, to take into consideration the findings of the IARC as regards the potential carcinogenicity (EFSA, 2015b, p. 2).

In October 2015, EFSA, together with EU Member States, finalised the risk assessment and peer review that updated the scientific conclusions of the toxicity of glyphosate. The conclusions of EFSA were based on - and followed - the peer review results of the hazard identification and initial risk assessments conducted by the authority of the rapporteur Member State Germany, the German Federal Institute for Risk Assessment (BfR). The context of the peer review followed the requirements specified in the Commission Regulation (EU) No 1141/2010 amended by Commission Implementing Regulation (EU) No 380/2013 (EFSA, 2015b, p. 1).

Following the evaluation of BfR, in 2015, EFSA and EU Member States finalised the re-assessment of the toxicity of glyphosate (EFSA, 2015b). The re-assessment of the risks posed by glyphosate was part of the standard European Union pesticide renewal process. In line with Article 12 of Regulation (EC) No 1107/2009, EFSA carried out an assessment of glyphosate, considering the technical specifications provided by the applicants from Glyphosate Taskforce (EFSA, 2015e, p. 5). The risks of glyphosate were assessed in the following areas: mammalian toxicity; residues; environmental fate and behaviour; ecotoxicology (birds and mammals); and environmental compartments (soil, ground water, surface water and sediment, air).

EFSA assessed the risks of glyphosate to human health by relying on research in the areas of mammalian toxicology and ecotoxicology and, in contrast to the IARC evaluation, concluded that "glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential" (EFSA, 2015b, p. 2). EFSA also reached the conclusion that glyphosate is not classified as carcinogenic or toxic for reproduction (see table below).

Glyphosate: EFSA updates toxicological profile

"In contrast to the IARC evaluation, the EU peer review experts, with only one exception, concluded that glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential according to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP Regulation). Glyphosate is not classified or proposed to be classified as carcinogenic or toxic for reproduction category 2 in accordance with the provisions of Regulation (EC) No 1272/2008 (harmonised classification supported by the present assessment), and therefore, the conditions of the interim provisions of Annex II, point 3.6.5 of Regulation (EC) No 1107/2009 concerning human health for the consideration of endocrine disrupting properties are not met." (EFSA 2015b, p. 2-3)

Unlike the IARC and JMPR, EFSA assessed not only the cancer risks of glyphosate, but their scientific conclusions also included considerations for the following: residues; environmental fate and behaviour; and ecotoxicology (birds and mammals), that are briefly introduced below:

- Based on the existing information, EFSA proposed residue definitions for monitoring and risk assessment for plant and animal commodities. "These residue definitions were proposed considering the metabolism observed in conventional and in glyphosate-tolerant GM [Genetically Modified] plants. Based on the representative uses, that were limited to conventional crops only, chronic or acute risks for the consumers have not been identified" (EFSA 2015b, p. 3). Furthermore, EFSA made relevant conclusions and suggestions: "The toxicity of glyphosate needs to be redefined. An acute reference dose (ARfD) of 0.5 mg/kg of body weight has therefore been proposed, the first time such a safety measure has been introduced for glyphosate. EFSA will use this ARfD during its review of the maximum residue levels for glyphosate,

which will be carried out in cooperation with Member States in 2016. The acceptable operator exposure level (AOEL) has also been set at 0.1 mg/kg body weight per day and an acceptable daily intake (ADI) for consumers has been set in line with the ARfD at 0.5 mg/kg body weight per day" (EFSA, 2015d, p. 1).

- Concerning the scientific conclusions on the fate and behaviour in the environment, EFSA concluded that further information is required to assess the "contamination route through run off (especially in situations where application to hard surfaces might occur) and subsequent surface water contamination and bank infiltration to groundwater" (EFSA 2015b, p. 3).

- Concerning the scientific conclusions on ecotoxicology, EFSA concluded that "for aquatic organisms, the risk was considered low. The risk for bees, non-target arthropods, soil macro- and micro-organisms and biological methods for sewage treatment was considered low. The risk to non-target terrestrial plants was considered low, but only when mitigation measures are implemented" (EFSA 2015b, p. 3).

More recently (September 2017), EFSA published one more risk assessment on glyphosate, in which it addressed the potential endocrine activity of glyphosate. The Authority's assessment concluded that "the weight of evidence indicates that glyphosate does not have endocrine disrupting properties" (EFSA, 2017g, p.1).

The scientific conclusions of EFSA regarding mammalian toxicity, residues, environmental fate and behaviour, ecotoxicology (birds and mammals) and the potential endocrine activity of glyphosate were based on a risk-based approach, i.e. weight-of-evidence (WoE) assessment approach, meaning that EFSA considered a wide range of scientific evidence, including academic research as well as industry research. EFSA reached the conclusion that glyphosate does not cause cancer in humans and is unlikely to be genotoxic. 27 out of 28 EU Member State experts agreed with the EFSA-endorsed peer review of glyphosate (with the exception of Sweden which was in favour of another classification).

European Chemicals Agency (ECHA)

ECHA is in charge of labelling and classifying substances and chemicals under Regulation (EC) No 1272/2008. The Committee for Risk Assessment (RAC) is responsible for presenting information related to the attributed risk of chemicals and other substances for humans, animals and the environment. Their advice is directly forwarded to the European Commission. The approval of the use of glyphosate was about to expire in the EU and therefore a new assessment of the substance was needed in order to decide whether or not an extension of the licence to be given by the European Commission. This was done through harmonised classification and labelling within the EU.
In June 2016, the European Commission decided to prolong the registration of glyphosate in the EU for 18 months (Regulation (EU) 2016/1056). The extension was made to give time for the European Chemicals Agency (ECHA) to carry out an independent hazard

assessment of glyphosate. It is important to note that the assessment by RAC was only focussed on the potential danger caused by a substance and did not take into account the prevalence and exposure of humans and animals to the substance (this part was covered in the scientific output of EFSA): "The classification is based solely on the hazardous properties of the substance. It does not take into account the likelihood of exposure to the substance and therefore does not address the risks of exposure. The risks posed by exposure are considered, for example, when deciding whether to renew the approval of glyphosate as a pesticide in accordance with the EU's Plant Protection Product Regulation (Regulation (EC) N° 1107/2009)" (ECHA, 2017b). This implies that both ECHA and the IARC conducted hazard assessment of glyphosate, while EFSA and other regulatory bodies discussed in this chapter focus on the risk assessment of glyphosate (see also EFSA, 2016e).

In March 2017, ECHA's Committee for Risk Assessment (RAC) provided an additional *hazard classification* associated to toxicity results from prolonged or repeated exposure to glyphosate. The ECHA's evaluation of glyphosate was carried out through public consultations. The Agency's consultations involved a wide range of toxicological studies that may or may not have been published (ECHA, 2017b). In its scientific output, RAC concluded that there was not enough scientific evidence and information to confirm a carcinogenicity hazard classification of glyphosate. ECHA communicated that the existing scientific scholarship do not give sufficient confidence to the criteria to classify glyphosate as toxic for reproduction, as a carcinogen or mutagen under the CLP Regulation. However, in its classification of glyphosate, RAC published their results concluding that glyphosate causes (1) serious eye damage and (2) is toxic to aquatic life with long lasting effects. However, ECHA scientific opinion identified glyphosate as not carcinogenic to humans (ECHA, 2017b).

Glyphosate not classified as a carcinogen by ECHA

"ECHA's Committee for Risk Assessment (RAC) agrees to maintain the current harmonised classification of glyphosate as a substance causing serious eye damage and being toxic to aquatic life with long-lasting effects. RAC concluded that the available scientific evidence did not meet the criteria to classify glyphosate as a carcinogen, as a mutagen or as toxic for reproduction" (ECHA, 2017b).

While the IARC assessed only the carcinogenic properties of glyphosate, the final evaluation of RAC and BAuA (the German Federal Institute for Occupational Safety and Health) was based on both: (1) Human Health Hazard Assessment and (2) Environmental hazard assessment (BAuA, 2016). Alongside its conclusions on the carcinogenic properties of glyphosate, RAC and BAuA arrived at the following conclusions regarding environmental hazard assessment: "Glyphosate fulfils the criteria for classification as Aquatic Chronic 2" (BAuA, 2016, p. 134). For more information on labelling and classifying substances and chemicals and the criteria for classification followed at the EU level, please see Regulation (EC) No 1272/2008.

United States Environmental Protection Agency (US EPA)

The United States Environmental Protection Agency (US EPA) was founded in 1970. Its mission is to "protect human health and the environment" (US EPA, 2018d). It provides assistance to the Legislative and the Executive Powers of the United States in framing policies that protect human health and the environment.

In September 2016, the US EPA re-assessed glyphosate (the carcinogenic effects glyphosate could have) as part of its Registration Review program (US EPA, 2016). In this particular scientific output (i.e., Glyphosate Issue Paper), the US EPA focussed on the evaluation of carcinogenic potential of glyphosate. The US EPA used a weight-of-evidence approach to re-assess the carcinogenicity of glyphosate. The EPA's Office of Pesticide Programs concluded that glyphosate does not cause cancer. In "Glyphosate Issue Paper", a 227-page peer review investigation which used more than 25 previous investigations (from 1975 onwards) on the potential effects of glyphosate, the US EPA concluded that "the available data […] clearly do not support the descriptors 'carcinogenic to humans', 'likely to be carcinogenic to humans' or [the existence] of 'inadequate information'" (US EPA, 2016).

Glyphosate Issue Paper: Evaluation of Carcinogenic Potential

"The available data at this time do not support a carcinogenic process for glyphosate. Overall, animal carcinogenicity and genotoxicity studies were remarkably consistent and did not demonstrate a clear association between glyphosate exposure and outcomes of interest related to carcinogenic potential. In epidemiological studies, there was no evidence of an association between glyphosate exposure and numerous cancer outcomes." (US EPA, 2016, p. 140)

In 2018, the US EPA will release its new risk assessment of glyphosate (US EPA, 2017d). However, the draft human health risk assessment and the ecological risk assessment are already available. As regards the human health risk assessment, the US EPA provided hazard characterisation, dietary (food and water) risk assessment, residential and non-occupational exposure and risk assessment, aggregate risk assessment, and occupational risk assessment. The US EPA states "The Agency's assessment found no other meaningful risks to human health when the product is used according to the pesticide label" (US EPA, 2017d). The conclusion was drawn following the evaluation of dietary, residential/non-occupational, aggregate, and occupational exposures. In addition, the US EPA conducted "an in-depth review of the glyphosate cancer database, including data from epidemiological, animal carcinogenicity, and genotoxicity studies" (US EPA, 2017d).

In its ecological risk assessment, the US EPA found that there is a "potential for effects on birds, mammals, and terrestrial and aquatic plants" (US EPA, 2017d). For additional information, please see the conclusions of the US EPA of draft ecological risk assessment (2018c).

Health Canada's Pest Management Regulatory Agency (PMRA)

The main objective of the PMRA when regulating pesticides is to protect the health of Canadians and the environment (PMRA, 2017). All pesticides need to be registered by the

PMRA. In April 2015, the PMRA re-assessed glyphosate as part of its standard regulatory procedure. The re-assessment concluded that glyphosate-containing products do not pose any risks to human health and the environment if they are used according to the directions on the label (PMRA, 2017) (see table below).

Core conclusions of the PMRA's risks to human health and the environment
Health Considerations:

- "Products containing glyphosate acid are unlikely to affect human health when used according to label directions.
- Residues in Food and Water: Dietary risks from food and water are not of concern.
- Risks in Residential and Other Non-Occupational Environments:
    - Non-occupational risks are not of concern when used according to label directions.
    - Non-occupational risks from bystander dermal exposure are not of concern.
- Occupational Risks from Handling Glyphosate:
    - Occupational risks to handlers are not of concern when used according to label directions.
    - Post application risks are not of concern for all uses.

Environmental Considerations:

- When used according to proposed label directions, glyphosate products do not pose an unacceptable risk to the environment. Labelled risk-reduction measures mitigate potential risks posed by glyphosate formulations to non-target plants and freshwater/marine/estuarine organisms." (PMRA, 2015)

In the re-examination, the PMRA assessed the risks for human health from glyphosate in the drinking water, food and occupational exposure, as well as the risks for the environment (PMRA, 2017). In the assessment, the PMRA looked at both the active ingredients and the formulated product. The assessment was performed on the basis of information from the producer of the product, as well as information found in scientific literature (PMRA, 2017).

Proposed Re-evaluation Decision PRVD2015-01, Glyphosate

"After a re-evaluation of the herbicide glyphosate, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the Pest Control Products Act and Regulations, is proposing continued registration of products containing glyphosate for sale and use in Canada.
An evaluation of available scientific information found that products containing glyphosate do not present unacceptable risks to human health or the environment when used according to the proposed label directions." (PMRA, 2015)

Canada has specified the MRLs for glyphosate for a wide range of products. Residues in all other agricultural commodities, including those approved for treatment in Canada but without a specific MRL, are regulated under Subsection B.15.002(1) of the Food and Drug Regulations, which says that residues should not exceed 0.1 ppm (PMRA, 2017). The final conclusion of the re-assessment is that glyphosate cannot be considered genotoxic and does not pose an extra risk for cancer in humans. Therefore, the PMRA has granted continued registration of products containing glyphosate with requirements of additional label updates to further protect human health and the environment; to comply with this decision the manufacturer needs to change labels within 24 months of the decision (PMRA, 2017).

In terms of environmental risk assessment of glyphosate, the PMRA concluded that "In the terrestrial environment the only area of risk concern identified from the available data was for terrestrial plants and therefore spray buffer zones are required to reduce exposure to sensitive terrestrial plants.

Glyphosate formulations pose a negligible risk to freshwater fish and amphibians, but may pose a risk to freshwater algae, freshwater plants, marine/estuarine invertebrates and marine fish if exposed to high enough concentrations. Hazard statements and mitigation measures (spray buffer zones) are required on product labels to protect aquatic organisms." (PMRA, 2015)

When the PMRA conducts a risk assessment or – in the case of glyphosate – a pesticide re-evaluation, they consider the potential risks and the value of pesticide products to ensure they meet modern standards established to protect human health and the environment (PMRA, 2017). The risk assessment is based on data from registrants, published scientific reports, information from other regulatory agencies. After a science-based assessment, it has been decided by the PMRA that, when glyphosate is used according to the prescription, the products containing the product are not a concern to human health and the environment. The PMRA has set MRLs and these requirements are set at levels well below the amount that could pose a health concern (PMRA, 2017).

Environmental Protection Authority of New Zealand (NZ EPA)

Glyphosate is widely used in New Zealand, which is why the sale and use of glyphosate is regulated under the Agricultural Compounds and Veterinary Medicines (ACVM) Act 1997 and the Hazardous Substances and New Organisms (HSNO) Act 1996 (MPI, 2015). The ACVM Act makes sure that no agricultural compound can be used in New Zealand unless it is authorised by or under this Act (MPI, 2015). The Ministry for Primary Industries (MPI) has established thresholds and criteria for public health, trade, safety and security, and these criteria were established on the basis of international practices (MPI, 2015).

In August 2016, the Environmental Protection Authority of New Zealand (NZ EPA) completed an evaluation of the available evidence for carcinogenicity caused by exposure to glyphosate. The Authority concluded that glyphosate was unlikely to cause cancer in humans (NZ EPA, 2016) (see table below).

Glyphosate Review

"The review concluded that glyphosate is unlikely to be carcinogenic to humans or genotoxic (damaging to genetic material or DNA) and should not be classified as a mutagen or carcinogen under the HSNO Act." (NZ EPA, 2016)

The different risks that were tested are needed for the product registration under the ACVM Act (MPI, 2018). This means that a thorough scientific assessment of chemistry and manufacturing information, animal and plant safety, and residues in food was carried out. Furthermore, the NZ EPA also looked at the toxicity levels of glyphosate. In this case, MPI agrees with the JMPR, stating that, for glyphosate, there are very low toxicity levels, meaning that glyphosate does not form a risk on the basis of the ACVM act.

The MPI has adopted the same conclusion after careful review and its own review of the dietary risks of glyphosate to the New Zealand public (MPI, 2018). The MPI does not agree with the IARC's view that glyphosate would be a risk to consumers and users. If used in line with the approved label directions, glyphosate complies with the New Zealand maximum residue limits and hence is not harmful to humans (MPI, 2018). Furthermore, the MPI emphasises that the toxicity and dietary risks of glyphosate have been reviewed by various other organisations, like the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO) who concluded that glyphosate is of very low toxicity.

Australian Pesticides and Veterinary Medicines Authority (APVMA)

The Australian Pesticides and Veterinary Medicines Authority (APVMA) was established in 1993 as a means by which agricultural and veterinary chemical products could be registered on a centralised system (APVMA, 2017). Any product that contains glyphosate needs to be registered for use in Australia; in order to be registered, all the products need to have been tested through a robust chemical risk assessment process to check that they are safe for use. A chemical risk assessment process means that both a hazard assessment and an exposure assessment have been conducted by the APVMA. These assessments are similar to the tests conducted in other countries: the APVMA uses a risk-based, weight-of-evidence assessment, which considers the full range of risk, like studies of cancer risks, minimisation of human exposure through instructions for use and safety directions (APVMA, 2017).

In 2016, the APVMA completed a "robust chemical risk assessment process", concluding that "the use of glyphosate in Australia does not pose a cancer risk to humans" (APVMA, 2017). The review of glyphosate had two phases; the first identified which studies used in IARC's initial report "should be reviewed in more detail", whilst the second stage "involved a detailed assessment of those studies". Generally speaking, the APVMA "uses a risk-based, weight-of-evidence assessment, which considers the full range of risks […] and how human exposure can be minimised". Furthermore, the APVMA's assessment of glyphosate solely concentrated on "the potential of glyphosate alone to cause cancer", as this was the IARC's focus and the APVMA focussed on the aspects of glyphosate risks

assessed by the IARC. The APVMA assessed risks including studies of cancer risk through hazard assessment and exposure assessment, concluding that "products containing glyphosate are safe to use as per the label instructions" (APVMA, 2017). For more detailed conclusions, please consult the table below.

Final regulatory position of the Australian Pesticides and Veterinary Medicines Authority (APVMA)

- "exposure to glyphosate does not pose a carcinogenic or genotoxic risk to humans
- there is no scientific basis for revising the APVMA's satisfaction that glyphosate or products containing glyphosate:
  - would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues;
  - would not be likely to have an effect that is harmful to human beings;
  - would not be likely to have an unintended effect that is harmful to animals, plants or things or to the environment;
  - would be effective according to criteria determined by the APVMA by legislative instrument, and
  - would not unduly prejudice trade or commerce between Australia and places outside Australia.
- there are no scientific grounds for placing glyphosate and products containing glyphosate under formal reconsideration
- the APVMA will continue to maintain a close focus on any new assessment reports or studies that indicate that this position should be revised
- there are no scientific grounds for placing glyphosate and products containing glyphosate under formal reconsideration." (APVMA, 2017, p. 9)

1.3 Agencies with inconclusive reports

French Agency for Food, Environmental and Occupational Health Safety (ANSES)

The assessment of glyphosate was conducted by the French Agency for Food, Environmental and Occupational Health Safety (ANSES) after several assessments were carried out at the European level when the substance needed a renewed approval. However, the assessment conflicted with the views of the IARC, who stated that glyphosate should be viewed as probably carcinogenic to humans (ANSES, 2015). In 2015, ANSES was asked by French authorities to conduct an expert appraisal on the basis of the monograph issued by the IARC (ANSES, 2016a). The expert appraisal was carried out by the French standard NF X 50-1104 (ANSES, 2016). Tasked with this request, the Emergency Collective Expert Assessment Group (GECU) included four experts on glyphosate and expertise in carcinogenicity, mutagenicity, and epidemiology (ANSES, 2016b). The request

[4] Please read more about the French quality standards and commitments in the following link: https://www.anses.fr/en/content/statement-anses-quality-policy-and-quality-commitment

for expert appraisal was carried out by GECU and with the scientific participation of ANSES. GECU did not have the time to go through all the regulatory reports about glyphosate that had been published by either the BfR or the IARC. Thus, they concentrated on a select number of reports provided by ANSES (ANSES, 2015).

GECU analysed the reports in order to explain the different conclusions reached by the EU (EFSA and ECHA's RAC) versus the IARC on whether or not glyphosate can be considered carcinogenic (ANSES, 2016b). GECU suggested that the results of the epidemiological studies are not consistent: there have been cases where bias or lack of power could be identified. Furthermore, the epidemiological results are not consistent because exposure to glyphosate is not indicated clearly (ANSES, 2016b). ANSES stated that the data shows now that glyphosate has limited risks to humans and animals (ANSES, 2016b). It must be said that, due to the limited time available for the expert appraisal, GECU and ANSES could only focus on a limited amount of studies due to the high variety of publications available (ANSES, 2016b). They chose to focus on the research by the IARC and European renewal assessment reports. The evidence illustrates that the level of carcinogenicity can be considered too limited in humans to impose a strict classification. However, due to the limited level of evidence, the research should be reclassified (ANSES, 2016a).

ANSES stated that it cannot reclassify glyphosate due to the limitations of the research, which in its turn is due to the absence of a detailed analysis. Thus, ANSES based their conclusion on reviewing the research of peers. On the 12th of December 2015, ANSES concluded that glyphosate may need to be classified as a suspected human carcinogen and that ECHA should review their classification. As discussed above, in 2017, ECHA scientific opinion identified glyphosate as not carcinogenic to humans (ECHA, 2017).

2. 2,4-D

2,4-Dichlorophenoxyacetic acid (i.e., 2,4-D) is an extensively used herbicide that controls broadleaf weeds including: "a variety of field, fruit and vegetable crops, and turf, lawns, rights-of-way, aquatic sites and forestry sites" (US EPA, 2017a). 2,4-D is one of the oldest and most broadly accessible herbicides in the world: it has been commercially available since 1945 and is currently produced by many chemical companies because the patent on it has expired.

The section provides a summary of the scientific findings of relevant regulatory agencies concerning 2,4-D. The scientific conclusions of the IARC, EFSA and the US EPA are introduced and discussed in this section. The IARC has conducted a hazard classification of the herbicide 2,4-D and concluded that the substance should be classified as 'possibly carcinogenic to humans' (2B), whereas other independent agencies (including EFSA and the US EPA) conducted risk assessments of 2,4-D concluding that 2,4-D is unlikely to be a human carcinogen.

In a nutshell, the core agreements and disagreement between IARC and other regulators are the following. The IARC and regulatory bodies worldwide agree with the finding that there is "inadequate evidence" in humans. For instance, the following agencies mandated

with protecting human health have reached the same conclusion: The United States Environmental Protection Agency (2007; 2012; 2014c), the European Food Safety Authority (2014a), the World Health Organization (1996; 2008) and more than 90 other countries (according to IARC (2016a)). These regulatory bodies and agencies have consistently concluded that the herbicide 2,4-D does not present a human cancer risk. This is in line with the conclusion of the IARC stating that epidemiological studies did not indicate strong or stable increases in risk of [non-Hodgkin's lymphoma] NHL or other cancers in relation to 2,4-D exposure (IARC, 2016a).

However, the IARC and other regulatory agencies disagree about the difference between hazard classification and risk assessment. The IARC have communicated that "the Monographs Programme identifies cancer hazards even when risks are very low at current exposure levels" (IARC, 2016a). On the contrary, the US EPA and other national and supranational regulatory bodies regard hazard classification as one step of a multiple-step process. To illustrate, in March 2016, the Health Canada's Pest Management Regulatory Agency (PMRA) issued a scientific evaluation of 2,4-D, in which the PMRA considered the IARC findings, and determined: "The IARC hazard classifications are not health risk assessments and the levels of human exposure, which determine the actual risk, are not taken into account in the IARC assessments." (PMRA, 2016). The IARC disagrees with such conclusions (the same disagreement applied in the glyphosate case).

In short, the relevant regulatory agencies have concluded that 2,4-D does not cause cancer in humans. The US EPA classified 2,4-D as 'not likely to be carcinogenic to humans' (US EPA, 2014). In 2008, the PMRA carried out a re-evaluation of 2,4-D and concluded that 2,4-D meets the health and safety standards of Canada. Furthermore, Canadian regulators emphasise that no other international regulatory body (except the IARC) regards 2,4-D to be a human carcinogen. The PMRA concluded that the herbicide "2,4-D does not increase the risk of cancer and can be used safely by homeowners, provided label directions are followed" (Health Canada, 2009). In 2015, following the peer review of the initial risk assessments carried out by the Rapporteur Member State Greece, for the pesticide active substance 2,4-D, EFSA reached the following conclusion: 2,4-D is unlikely to have a genotoxic potential or pose a carcinogenic risk to humans. EFSA could not identify any conclusive association can be established between exposure to phenoxy-herbicides (including 2,4-D acid) and human carcinogenicity (EFSA, 2014a).

The remainder of this section discusses the scientific findings of the three regulatory bodies – i.e., the IARC, EFSA, US EPA – in more detail.

1.4 Agencies concluding that 2,4-D poses a carcinogenic hazard

The International Agency for Research on Cancer (IARC)

As the IARC deals solely with cancer related hazard classification, this section is created to assess the hazards associated with 2,4-D in terms of carcinogenic properties.

The IARC reviewed the latest scientific literature and reached the conclusion that the herbicide 2,4-D should be classified as 'possibly carcinogenic to humans' (group 2B) (IARC, 2017a). Such a classification is one step below the more definitive "probably carcinogenic" category (e.g., the conclusion reached in the glyphosate case), however, two steps above the "probably *not* carcinogenic" category. The core justification for classifying 2,4-D as "possibly carcinogenic to humans" was the lack of data. The IARC stated that there is "inadequate evidence in humans and limited evidence in experimental animals" of relationship between 2,4-D and cancer (IARC, 2015b, p. 1). Furthermore, the IARC concluded that epidemiological studies provided "strong evidence that 2,4-D induces oxidative stress […] and moderate evidence that 2,4-D causes immunosuppression" (IARC, 2015b, p. 1). However, the IARC found that there is not an association between leukaemia (blood cancer) and 2,4-D: "epidemiological studies did not find strong or consistent increases in risk of NHL (non-Hodgkin lymphoma) or other cancers in relation to 2,4-D exposure." (IARC, 2015b, p. 1, see also IARC, 2017a).

"The herbicide 2,4-D was classified as possibly carcinogenic to humans (Group 2B), based on inadequate evidence in humans and limited evidence in experimental animals. There is strong evidence that 2,4-D induces oxidative stress, a mechanism that can operate in humans, and moderate evidence that 2,4-D causes immunosuppression, based on in vivo and in vitro studies. However, epidemiological studies did not find strong or consistent increases in risk of NHL or other cancers in relation to 2,4-D exposure." (IARC, 2015b, p. 1)

1.5 Agencies concluding that 2,4-D is unlikely to pose a carcinogenic risk

European Food Safety Authority (EFSA)

2,4-D has been approved for usage in the EU by Commission implementing Regulation (EU) No 540/2011. This regulation states that 2,4-D has been approved on the 1st of October 2002, with the date of expiration of approval being the 31st of December 2015. Therefore, renewal of the application was imminent.

Commission Regulation (EU) No 1141/2010[5] specifies the procedures for the renewal of the approval of active substances and establishes the list of those substances. 2,4-D is one of the substances listed in the Regulation. Following the relevant procedure, the Rapporteur Member State (Greece) and the co-Rapporteur Member State (Poland) provided their hazard identification on 2,4-D. Consequently, EFSA initiated the peer review in March 2013. EFSA was requested to issue "a conclusion on whether 2,4-D can be expected to meet the conditions provided for in Article 4 of Regulation (EC) No 1107/2009 of the European Parliament and of the Council" (EFSA, 2014a, p. 5).

EFSA's conclusion report summarises the outcomes of the peer reviews of the risk assessment on the active substance in relation to its typical uses as an herbicide on wheat,

[5] As amended by Commission Implementing Regulation (EU) No 380/2013.

barley, oat, rye triticale (cereals) and maize. In September 2014, EFSA made conclusions in regard to 2,4-D toxicity to mammals, the impact of residue left behind, 2,4-D environmental impacts and its potential ecotoxicological effects.

The overall conclusion from the evaluation is that plant protection products containing 2,4-D fulfil the safety requirements laid down in Regulation (EC) No 1107/2009 (EFSA, 2014a). The review has concluded that under the proposed conditions of use of 2,4-D there are no unacceptable effects on the environment. Furthermore, 2,4-D is not classified as a carcinogenic substance.

In its conclusion, EFSA notes that there is evidence of possibly adverse endocrine effects on the hormone system, which also might affect other organ systems. With regards to the ecotoxicological potential endocrine activity of 2,4-D, the scientific conclusion of EFSA does not identify specific concerns for fish and birds.

US Environmental Protection Agency (US EPA)

In 2005, the United States Environmental Protection Agency released a Registration Eligibility Decision (RED) on the chemical 2,4-D (US EPA, 2005). The RED included a comprehensive risk assessment (covering both human health risk and environmental risk); a risk management, reregistration, and tolerance re-assessment decision; and guidelines for registrants. The risk assessment was based on information from 1992 through 2000 for agriculture and 1993 through 1999 for non-agriculture risk. The studies used for assessment were based on the required target database supporting the use patterns of the currently registered products and additional information received from the 2,4-D Task Force II (comprised of leading industry actors such as Dow Chemical Company).

Action 4(g)(2)(A) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) calls for the US EPA to determine, after submission of relevant data concerning an active ingredient, whether or not products containing the active ingredient are eligible for re-registration. Based on a review of data and of public comments on the Agency's assessments for the active ingredient 2,4-D, the EPA claimed to have sufficient information on the human health and ecological effects of 2,4-D to make decisions as part of the tolerance re-assessment process under the Federal Food, Drug, and Cosmetic Act (FFDCA) and re-registration process under FIFRA (US EPA, 2005). To combat the numerous negative ecological conclusions of the assessment, the US EPA required the conception of plans to control spray drift, updated labelling, and a maximum turf rate of 1.5 lbs/Acre (down from 2 lbs/Acre). *The Agency has determined that 2,4-D containing products are eligible for re-registration provided that*: (1) current data gaps and confirmatory data needs are addressed; (2) the risk mitigation measures outlined in this document are adopted, and (2) label amendments are made to implement these measures. Under the mandate of this RED, 2,4-D was successfully re-registered and approved for both domestic and industrial use. There is not yet a date set for another assessment, however, the US EPA is obliged to re-evaluate all registered pesticides at least once every 15 years.

3. Bentazone

3-isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one 2,2-dioxide, more commonly known as bentazone, is a chemical used in pesticides and herbicides. Bentazone is used as a selective contact post-emergence herbicide which is absorbed through the leaves of target plants (Hartley and Kidd, 1983). Target plants are broadleaved weeds and sedges. Furthermore, bentazone is used for use on a variety of lentil crops (broad beans, field beans, runner beans, navy beans, combining peas, vining peas), as well as potatoes.

The section provides a summary of the scientific findings of relevant regulatory agencies and bodies concerning bentazone. The three agencies that have conducted risk assessments on bentazone and are covered in this section are EFSA, the US EPA and JMPR.

European Food Safety Authority (EFSA)

The active characteristics of bentazone were first managed by Commission Regulation (EU) No 1141/2010[6], which characterises bentazone as a second-group of active substances. According to Article 16 of this Regulation, if mandated, EFSA needs to conclude if the active substance meets the conditions proposed in the above regulation, specifically in the areas of mammalian toxicology, residues, environmental fate and behaviour, and ecotoxicology. The risk assessment was initiated following the RAR (the Netherlands) for consultation of the Member States and the applicants BASF SE and AgriChem BV (EFSA, 2015a, p. 2).

In 2015, EFSA issued its scientific opinion on bentazone. EFSA identified many data gaps and stated that the assessment could not be fully finalised. EFSA has identified data gaps in the following areas which are further explained below (for more detailed information, see (EFSA, 2015a, p. 2)):

- An analytical method in terms of monitoring all the components of the residue definition in surface water;
- In the mammalian toxicology area;
- Potential endocrine disrupting properties;
- Risks to consumers;
- Toxicological data allowing to establish reference values for the metabolite 6-hydroxy-bentazone.

More specifically, EFSA stated that "in the area of identity, physical/chemical/technical properties and methods of analysis *a data gap was identified* for an analytical method for monitoring all the components of the residue definition in surface water" (EFSA, 2015a, p. 2). Furthermore, *data gaps* were acknowledged in the mammalian toxicology area, which did not allow to "address the relevance of the individual impurities present in the technical specifications of both applicants" (EFSA, 2015a, p. 2). As a result, EFSA proposed to classify

[6] as amended by Commission Implementing Regulation (EU) No 380/2013

bentazone as toxic for reproduction category 2 in accordance with the provisions of Regulation (EC) No 1272/2008.

In addition, EFSA concluded that "an endocrine- mediated mode of action could not be ruled out regarding the critical effects observed in the developmental toxicity study in rats", as *a data gap was identified* and therefore the assessment could not be completed (EFSA, 2015, p. 2). Furthermore, *a data gap* was also "identified for further toxicological data allowing to establish reference values for the metabolite 6-hydroxy-bentazone as it is included in the residue definition for risk assessment" (EFSA, 2015a, p. 2). In a similar vein, the consumer risk assessment is not completed because "the proposed residue definitions for risk assessment in plants and for enforcement in livestock are considered as provisional due to *the identified data gaps*" (EFSA, 2015a, p. 2).

Finally, the groundwater exposure assessment for bentazone could not be finalised by EFSA because *of the data gaps*. In addition, the National Institute for Public Health and the Environment (RIVM) (the Netherlands, Rapporteur Member State) reported to EFSA that residues of bentazone and other pesticides had been found in groundwater in concentrations above the drinking water threshold level (RIVM, 2015, p. 11), which led to questions on whether the regulations on these pesticides were strict enough. RIVM evaluated whether concentrations in groundwater under realistic worst-case conditions exceed the threshold limit in drinking water. The report found that bentazone failed to pass tests that are specific to the Netherlands. As a result, RIVM stated that "calculated annual average concentrations are minimally a factor of 20 above the criterion value" (RIVM, 2015, p. 70, for more information, please read the report issued by RIVM (2015)).

EFSA has concluded that there is *a high long-term* risk to mammals for the representative uses of bentazone applied to grass seed, grazing land and turf (EFSA, 2015a, p. 3). *A high acute and/or long-term risk* to birds and mammals was also concluded for several of the representative uses of bentazone. *A low risk* to all other groups of non-target organisms was concluded. However, according to EFSA, genotoxic, carcinogenic or neurotoxic effects are not produced by bentazone.

On the basis of the risk assessment of EFSA, in 2016, the European Commission suggested to renew the EU authorisation for bentazone herbicide until the 31st of January 2032 (its approval expired on the 30th of June 2017). However, at the same time, the Commission requested additional data confirming bentazone's safety, as EFSA identified many data gaps which resulted in the unfinalised risk assessment.

United States Environmental Protection Agency (US EPA)

The United States Environmental Protection Agency, or the US EPA, initially began to inquire about the safety of bentazone (or products containing bentazone) in 1972. The chemical was issued a registration standard by the US EPA in 1985 – requiring cautionary labels (US EPA, 1994). More information and studies were needed, prompting the US EPA

to require registrants to generate and submit further data (US EPA, 1994). Using the new data, the US EPA released a reregistration eligibility decision known as an RED in 1994. This document contains a risk assessment based on all new data since the original registration in addition to extensive studies particularly in regard to oral consumption and carcinogenic effects. The contents of the RED on bentazone are summarised below.

In terms of human risk assessment, bentazone is considered slightly acutely toxic for both skin contact and ingestion (US EPA, 1994). Furthermore, it is classified as a "Group E" carcinogen, meaning that there is no evidence of the substance leading to cancer. Some development toxicity effects were, however, observed in rodent tests. As stated before, dietary risks associated with the presence of bentazone on crops are not considered of concern by the US EPA (this is backed-up by residue tests). Based on estimates of exposure, the US EPA also determined that a minimum PPE (personal protective equipment) is required for handling the substance. Overall, however, worker risks are considered low (US EPA, 1994).

In terms of environmental risk assessment, surface runoff and leaching through soil are considered the main routes of dissipation for bentazone (US EPA, 1994). The largest concern here is contamination of drinking water, which prompted the US EPA to set a lifetime Health Advisory (HA) of 20 parts per billion (ppb), which it will likely increase to 200 ppb. Despite this, bentazone is not officially regulated under the Safe Drinking Water Act (SDWA), meaning that no Maximum Contaminant Level has been set. Further risks were identified in regard to the reproductive health of birds, which, though acute/subacute, is not seen as a major concern. Usage restrictions of the substance are designed to mitigate this impact. No hazard has been identified for aquatic animals or honeybees. Overall, the US EPA concluded that the "use of bentazone as an herbicide will not pose a serious environmental threat" (US EPA, 1994, p. 174).

In 1998, the EPA's Integrated Risk Information System conducted another review on bentazone which ultimately confirmed the RED's assessment (US EPA, 1998). In the following years, the US EPA revised its procedure concerning pesticide registration. Pesticides are to be reviewed every 15 years to ensure that the US EPA's risk assessments are in compliance with contemporary scientific studies. This process began for bentazone in 2010 and is still ongoing as the US EPA has not yet released a final review decision. Several risk assessment studies conducted during this review process are, however, already available. Notably, a preliminary human health risk assessment on sodium bentazone conducted in 2014 as a part of the registration review. The results from this risk assessment are summarised below:

- Reaffirmation of "Group E" non-carcinogenic chemical classification. In other words, this assessment also rules out cancer risk (US EPA, 2014c).
- Human ingestion of bentazone occurs when pesticide residue is found in plants, livestock, and drinking water (US EPA, 2014c).
- The US EPA provides recommendations for tolerance level of bentazone residue in commodities. The recommended tolerance levels are nearly identical to those established in older studies (US EPA, 2014c).

- The US EPA provides similar toxicology assessment drawing from animal studies similar to those that were conducted in the RED. Newer studies are also included that provide similar results with increased accuracy. The conclusion is again that dietary intake effects are negligible considering residue amounts (US EPA, 2014c).
- The only significant point of departure is in regard to the maximum application rate for specific crops. The RED specified a maximum of 2 lbs ai/a while this particular risk assessment recommended between 1 and 1.5 lbs ai/a depending on the crop (US EPA, 2014c).
- Further studies were also done on the potential for spray-drift exposure, which was not provided in the RED (US EPA, 2014c).

Since the scientific evaluation is only a preliminary health risk assessment to be used in the US EPA's registration review, it consists mostly of data. On the whole, it provides the US EPA with updated information that seems to imply that only a slight increase of caution might be appropriate. Consequently, the US EPA's stance – as reflected in their registration review decision – will likely be similar to the *status quo* established in the RED.

Joint FAO/WHO Meeting on Pesticide Residues (JMPR)

Bentazone was first assessed by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) in 1991, and then reviewed again in 1998; the most recent report in 2012 was the most updated risk assessment of bentazone in food. The Joint Meetings assess the hazard degree of bentazone in food, water, several grains, beans and animals, and arrive to the recommendation of dietary intake. In the 1991 meeting, the ADI was recommended to be 0–0.1 mg/kg bw on the basis of 9 mg/kg bw NOAEL per day. The level of acute toxicity in rats, guinea pigs and rabbits is characterised as low, and WHO has classified bentazone as slightly hazardous (JMPR, 1991). The 1998 report recommends a maximum residue level of 1 mg/kg for bentazone in dry peas, 0.1 mg/kg for bentazone in potatoes, 0.2 mg/kg for maize fodder, 0.07 to 1.14 mg/kg for alfalfa and 2 mg/kg for green alfalfa forage (JMPR, 1998). The ADI of 0–0.1 mg/kg bw is also reaffirmed in this meeting and the establishment for AfRD is ruled out.

Bentazone was reviewed again in 2012 as part of the periodic re-evaluation programme of the Codex Committee on Pesticide Residues (JMPR, 2012). The JMPR noted that since its last review in 2004, no relevant new studies have been produced. Furthermore, most of the studies do not fulfil with good laboratory practice (GLP) standards, as they were produced before implementation of GLP. The 2012 risk assessment was focussed on the effect of bentazone on rats and arrived at the conclusion that an ADI of 0–0.09 mg/kg bw derived from a NOAEL of 9 mg/kg bw per day change the effect on kidney and liver at 35 mg/kg bw per day (JMPR, 2012). The Meeting also concluded that bentazone is not teratogenic in rats or rabbits, and adverse health effect or poisoning symptoms are not identified in case of human exposure to bentazone (in manufacturing personnel and operators). However, it is reported that bentazone has potential impacts on foetuses, infants and children.

4. Neonicotinoid pesticides: clothianidin, imidacloprid, thiamethoxam

A suspicion that neonicotinoids were harmful to the environment first arose following the publication of the scientific articles published in the highly reputable scientific journal *Science*. Two teams of researchers (Henry et al. and Schneider et al.) concluded that "low levels of neonicotinoid pesticides can have significant effects on bee colonies" (EFSA, 2012). More specifically, Henry et al. suggested that "exposure of bees to sub-lethal doses of the active substance thiamethoxam causes a number of behavioural impairments in bees and, by altering their homing skills, may contribute to bee-colony weakening at a level likely to place the hive in a critical situation" (ANSES, 2012, p.1). The scientific studies had prompted national and EU risk regulators to seek for the further scientific and technical explanations from their regulatory agencies (see Alemanno, 2013; Bozinni, 2017; Rimkutė, 2015).

On the 23rd of March 2012, ANSES received a request from the French Directorate General for Food (DGAL) for scientific and technical support. One month later (on the 31st May 2012), ANSES issued its scientific assessment and a recommendation stating that a review of neonicotinoids (thiamethoxam, clothianidin, etc.) should be conducted at the European Union level based on new scientific data from recent studies (ANSES, 2012). In this context, ANSES and EFSA worked together and engaged in a collaborative process to exchange data.

In a similar vein, following publication of the studies in 2012, the European Commission issued a formal request to EFSA to compare the actual exposure of bees to neonicotinoids with the exposure levels used in the published research (European Commission, 2018a). In addition, EFSA was asked to determine whether the results could be applied to other neonicotinoids used for seed treatment. More specifically, the European Commission's mandate asked EFSA to evaluate the risks related to the use of clothianidin, imidacloprid and thiamethoxam as seed treatment or as granules, by exclusively focussing on:

- their acute and chronic effects on bee colony survival and development;
- their effects on bee larvae and bee behaviour;
- the risks posed by sub-lethal doses of the three substances.

This section maps the relevant regulatory agencies that provided risk assessments on neonicotinoid pesticides, focussing on the scientific outputs of EFSA, the US EPA) and the Canadian Pest Management Regulatory Agency (PMRA). The remainder of this section outlines which chemicals were analysed by the four agencies and provides an overview of the scientific conclusions reached.

European Food Safety Authority (EFSA)

On the 16th of January 2013, EFSA published its conclusion on the peer review of the pesticide risk assessment for bees for the active substance clothianidin (EFSA, 2013), imidacloprid (EFSA, 2013), thiamethoxam (EFSA, 2013). EFSA scientific experts have identified a number of risks posed to bees by the three neonicotinoid insecticides (EFSA, 2013). However, most of the variables and types of risk were marked as 'not finalised'. This

means that "there were no data, or insufficient data available to reach a conclusion / where there are no agreed risk assessment schemes available" (EFSA, 2013). The core scientific conclusions of EFSA are summarised in the table below.

"Where the risk assessments could be completed, EFSA, in cooperation with scientific experts from EU Member States, concluded the following for all three substances:

- Exposure from pollen and nectar: Only uses on crops not attractive to honey bees were considered acceptable.
- Exposure from dust: A risk to honey bees was indicated or could not be excluded, with some exceptions, such as use on sugar beet and crops planted in glasshouses, and for the use of some granules.
- Exposure from guttation: The only risk assessment that could be completed was for maize treated with thiamethoxam. In this case, field studies show an acute effect on honey bees exposed to the substance through guttation fluid." (EFSA, 2013)

In 2013, following the risk assessments carried out by EFSA, the European Commission imposed restrictions on the use of clothianidin, imidacloprid and thiamethoxam (see Regulation (EU) No 485/2013). The Commission restricted the use of plant protection products and treated seeds containing three of these neonicotinoids to protect honeybees. The regulation "prohibits the use of these three neonicotinoids in bee-attractive crops (including maize, oilseed rape and sunflower) with the exception of uses in greenhouses, of treatment of some crops after flowering and of winter cereals" (European Commission, 2018a).

On the 28th of February 2018, EFSA has published its new scientific conclusions on the neonicotinoid pesticides (clothianidin, imidacloprid and thiamethoxam) that update those published in 2013 (EFSA, 2018e). In the new scientific assessment, the Pesticides Unit of EFSA carried out an extensive data collection exercise to collect all the scientific evidence published since the previous evaluations. In its new scientific conclusions, EFSA confirmed its key scientific conclusions of 2013, i.e. overall clothianidin (EFSA, 2018j), imidacloprid (EFSA, 2018j) and thiamethoxam (EFSA, 2018j) pose a risk to bees.

The literature reviews covered not only honeybees (as it was the case in 2013), but also included bumblebees and solitary bees. The core conclusion of the scientific evaluation was the assessed neonicotinoid pesticides (clothianidin, imidacloprid and thiamethoxam) pose high risks to honeybees, bumblebees and solitary bees: "The conclusions on risk varied according to factors such as the bee species, the intended use of the pesticide and the route of exposure (residues in bee pollen and nectar; dust drift during the sowing/application of the treated seeds; and water consumption). However, taken as a whole the conclusions confirm that neonicotinoids pose a risk to bees" (EFSA, 2018j). The head of EFSA's Pesticides Unit, Dr. Jose Tarazona, noted: "There is variability in the conclusions, due to factors such as the bee species, the intended use of the pesticide and the route of exposure.

Some low risks have been identified, but overall the risk to the three types of bees we have assessed is confirmed" (EFSA, 2018e).

The most recent of EFSA's conclusions were shared with the European Commission and Member States who are in charge of risk management, i.e., the considerations of potential amendments to the current restrictions on the use of these pesticides. By the time of completing this study, those considerations are on-going.

United States Environmental Protection Agency (US EPA)

Following suspicions that neonicotinoid pesticides caused harm to bees, in 2012, in partnership with the PMRA, the US EPA started investigating those chemicals.

In 2016, the US EPA conducted studies on the active substances clothianidin, imidacloprid, thiamethoxam and their effects on pollinators, ecology and human health (US EPA, 2018e). In its preliminary risk assessments, the US EPA concluded that the chemicals could pose risks to bees (Wagman et al, 2017),[7] but further research indicated that these risks occurred only under certain circumstances, as such, the agency concluded that neonicotinoids (clothianidin, imidacloprid, thiamethoxam) did not pose a direct threat to bees. The US EPA will finalise its findings in 2018.

Canadian Pest Management Regulatory Agency (PMRA)

In 2012 and 2013 following reports of "bee deaths linked to exposure to the dust created from planting corn and soy seeds treated with neonicotinoids" (Health Canada, 2016). The government of Canada introduced new rules in 2014, in order "to reduce dust when planting this type of treated seed" (Health Canada, 2016). The agency reports that, as a result of "these new requirements in place, the number of reported bee deaths from pesticide exposure has been reduced by up to 80%"(Health Canada, 2016).

For the past years, the PMRA has worked together with the US EPA to conduct risk assessments on neonicotinoid pesticides. The agency conducted risk assessments on the active substances imidacloprid, clothianidin, and thiamethoxam, focussing on their effects on human health, the environment and pollinators (and further a special review of aquatic risks) (Health Canada, 2017b). The PMRA has concluded that imidacloprid poses risks for aquatic environments; it is still finalising its reports on the other substances (Health Canada, 2017a). So far, the agency states that neonicotinoids (imidacloprid, clothianidin, and thiamethoxam) do not pose risks to human health or pollinators if used according to the limits established in the legislation.

Having discussed the general scientific conclusions, the section further goes in-depth in the conclusions reached by EFSA, the US EPA and PMRA per active substance, focussing on the several agencies' findings regarding the three chemicals (clothianidin,

[7] Wagman, M., Mroz, R., Blankinship, A. and M. Koper, C. (2017). Preliminary Bee Risk Assessment to Support the Registration Review of Clothianidin and Thiamethoxam. Washington D.C.

thiamethoxam, imidacloprid). *Table 2* and the following sub-sections provide an overview of these conclusions.

Table 2: Regulatory agencies and their risk assessments of neonicotinoids

Object of risk assessment	Regulatory agency	Scientific findings	Conclusion and suggestive policy output
Clothianidin	EFSA (2013)	Two studies were used to determine the 'no observable effect concentration' (NOEC) values, the highest dose on which there is no negative effect noticed. For clothianidin, this was expressed as >= 40 µg a.s./kg diet.	Risks were identified in most types of crops, including cereals, maize, oilseeds, and sunflowers. From the finalised risks, acute dust exposure risk is the most notable.
	US EPA	Combined preliminary risk assessment of clothianidin and thiamethoxam. The EPA examined the two substances' impact on bees in three tiers.	No acute, chronic, or short-term aggregate risk estimates of concern for the registered uses of clothianidin exist.
	PMRA	Clothianidin did not cause cancer in laboratory animals and is non-genotoxic.	Clothianidin is unlikely to affect humans' health when used according to label directions.
Imidacloprid	EFSA	EFSA noted a LD50, the doses at which 50% of subjects dies, of 81 ng/bee. The NOEC based on mortality is <2.5 ng/bee, while an effect on habituation is reached at 0.1 ng/bee. Oral exposure levels are lower: LD50 at 3.7 ng/bee, NOEC at 1.2 ng/bee.	Risks were identified in most types of crops, including cereals, maize, oilseeds, and sunflowers. From the finalised risks, acute dust exposure risk is the most notable.

	US EPA	The threshold for imidacloprid in crops was '25 parts per billion'.	Crops below this level of 'nectar residue' do not pose risk.
	PMRA	A potential risk to bees was indicated for bee attractive crops associated with pre-bloom, during-bloom, and some post-bloom applications	Crops below this level of 'nectar residue' do not pose risk.
Thiamethoxam	EFSA	It is noted that, at 25 µg/kg sucrose solution, 2 out of 11 bees had not returned within 24 hours compared to 100% of the control bees	Acute risk for a number of crops from dust exposure was found. Risks stemming from maize and oilseed rape are labelled as acute.
	US EPA	MOEs were higher than identified concern (LOC 100)	No risk posed by the substance in any of the situations assessed
	PMRA	Some current uses of thiamethoxam are not expected to affect bees; however, there are some uses of thiamethoxam that may pose a risk of concern to bees	Mitigation measures are proposed to minimise potential exposure to bees, where necessary

Clothianidin

EFSA utilised two studies to determine the no observable effect concentration (NOEC) values, the highest dose of which there is no negative effect noticed (EFSA, 2013). For clothianidin, this was expressed as >= 40 µg a.s./kg diet. Although most of the results in the peer review research are "not [finalised]", risks were identified in most types of crops, including cereals, maize, oilseeds, and sunflowers. From the finalised risks, acute dust exposure risk is the most notable. Risks from nectar/pollen and guttation were largely "not [finalised]" either.

In its new scientific conclusions conducted in 2018, EFSA relied on extensive data which allowed the finalisation of the conclusions that were not completed in 2013. In the detailed and nuanced risk assessment of clothianidin, EFSA concluded that overall clothianidin

poses a high risk to honey bees and bumble bees across various seed treatments and across various tiers (EFSA, 2018j).

US EPA's final risk assessment on clothianidin is scheduled to be released in 2018. In its combined preliminary risk assessment of clothianidin and thiamethoxam, the US EPA examined the two substances' impact on bees in three tiers (US EPA, 2017).[8] In the first tier, it examined "risk quotient" to understand "acute and chronic risks" to individual bees. It concluded that risks for the bees existed in all uses ("foliar, soil and seed") in this tier. In the second tier, honey bee colonies were exposed to the "risks identified" in tier I. It concluded that similar level of risks also existed in this tier. In the third tier, there were "full field colony level studies" from "seed treatments". The effects in this tier were "transient or limited". In the US EPA's risk assessment of clothianidin's human health effects, the US EPA measured exposure through potential "dietary, food and drinking water" sources (US EPA, 2017e). For all three measures, the US EPA concluded that "no acute, chronic, or short-term aggregate risk estimates of concern for the registered uses of clothianidin exist" (US EPA, 2017).

The PMRA found that "clothianidin did not cause cancer in laboratory animals and is non-genotoxic", and as such "clothianidin is unlikely to affect humans' health when used according to label directions" (PMRA, 2013). The agency states that, if used according to the limits established in the country's legislation, the chemical is safe to use.

Imidacloprid

The acute and chronic toxicity of imidacloprid are determined on the basis of previous EFSA as well as INRA (the French National Institute for Agricultural Research) studies. In contact exposure, EFSA noted a LD50, the doses at which 50% of subjects dies, of 81 ng/bee (EFSA, 2013). The NOEC based on mortality is <2.5 ng/bee, while an effect on habituation is reached at 0.1 ng/bee. Oral exposure levels are lower: LD50 at 3.7 ng/bee, NOEC at 1.2 ng/bee.

Again, many of EFSA tests are marked as "not [finalised]". However, the acute risk from dust exposure for a range of crops is identified (EFSA, 2013). In its new scientific conclusions conducted in 2018, EFSA relied on an extensive data which allowed the finalisation of the conclusions that were not completed in 2013. In the detailed and comprehensive risk assessment of imidacloprid, EFSA concluded that, overall, imidacloprid poses a high risk to bees across various seed uses of the pesticide and across various tiers (EFSA, 2018j).

US EPA's final risk assessment on imidacloprid will be released in 2018. In its preliminary 'pollinator only' risk assessment in 2016, the agency examined the impact of imidacloprid on honey bees at individual and colony levels. It concluded that imidacloprid creates "risks" to their health (Cornell University, 2017). This risk, however, is determined by the "pollinating crops". The threshold for imidacloprid in crops was "25 parts per billion".

[8]Preliminary Bee Risk Assessment to Support the Registration Review of Clothianidin and Thiamethoxam. (2017, June 15). Retrieved December 20, 2017 from https://www.epa.gov/pesticides/epa-releases-four-neonicotinoid-risk-assessments .

Crops below this level of "nectar residue" do not pose said risk. Citrus and cotton were identified as crops posing significant risks.

The PMRA found that with this active substance "a potential risk to bees was indicated for bee attractive crops associated with pre-bloom, during-bloom, and some post-bloom applications" (US EPA and PMRA, 2013).

Thiamethoxam

In the scientific conclusions carried out in 2013, EFSA's risk assessment of thiamethoxam was mostly not finalised. However, it was noted that, "at 25 µg/kg sucrose solution, 2 out of 11 bees had not returned within 24 hours compared to 100% of the control bees" (EFSA, 2013). Moreover, an acute risk for a number of crops from dust exposure was found. Risks stemming from maize and oilseed rape are labelled as acute. In 2018, EFSA have reach more conclusive results that allowed to conclude that overall thiamethoxam poses a high risk to bees (EFSA, 2018j).

In its draft human health risk assessment of thiamethoxam, the US EPA looked at the "dietary, residential and spray drift exposures" (US EPA, 2017).[9] The EPA concluded that there was no risk posed by the substance in any of these situations. In general, it concluded that "MOEs were higher than identified of concern (LOC 100)".

The PMRA found that some current uses of thiamethoxam are not expected to affect bees; however, there are some uses of thiamethoxam that may pose a risk of concern to bees. As such, mitigation measures were proposed by the agency in December 2017 to minimise potential exposure to bees, where necessary (Health Canada, 2017).

II – Conclusion

What are the key issues and controversies concerning glyphosate, 2,4-D, bentazone, and neonicotinoid pesticides? What are the scientific conclusions and regulatory decisions regarding the aforementioned pesticides?

Glyphosate is used as an herbicide in many agricultural sectors. It was discovered and patented by Monsanto but since its patent has expired it has been manufactured by many chemical companies. The active substance has been assessed multiple times by European Union (EU) agencies as well as other agencies worldwide. There have been ongoing debates about the effects of glyphosate on humans regarding carcinogenic, endocrine disruptive and fertility hazards. In March 2015, the International Agency for Research on Cancer (IARC) classified glyphosate as 'probably carcinogenic to humans' (IARC, 2017d). This was followed by a public and political debate about the labelling, classification and renewal of the glyphosate licence. The European Food Safety Authority (EFSA) conducted a risk assessment of glyphosate and concluded that "glyphosate is unlikely to pose a

[9] Thiamethoxam. Draft Human Health Risk Assessment for Registration Review. (2017, December 5). Retrieved December 21, 2017 from https://www.epa.gov/pollinator-protection/schedule-review-neonicotinoids-pesticides;

carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential according to Regulation (EC) No 1272/2008" (EFSA, 2015b, p. 1). The scientific evaluation of glyphosate risks (at EFSA level) was conducted together with and supported by 27 Member States (with an exception of Sweden). Furthermore, independent regulatory authorities worldwide working outside the EU have reached the same scientific conclusions as EFSA. Regulatory bodies that reached the same scientific conclusion as EFSA include independent risk assessors based in the US, Canada, Australia, and New Zealand; their scientific conclusion has been supported and endorsed by the Joint Food and Agriculture Organization of the United Nations – World Health Organisation Meeting on Pesticide Residues (JMPR). In a similar vein, in 2017, the Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA) concluded that a link between glyphosate and cancer in humans cannot be established (ECHA, 2017). In addition, ECHA's scientific evaluation (based on their assessment of available information and existing scientific knowledge) was in line with EFSA and other national regulatory authorities' conclusions: glyphosate should not be categorised as a substance that causes genetic damage (mutagen) or disrupts reproduction. In November 2017, a qualified majority supporting the proposal by the European Commission to renew the approval of glyphosate for a period of 5 years was reached by the Appeal Committee. On the 12th of December 2017, the Commission adopted the act to renew the approval of glyphosate for 5 years (European Commission, 2018b).

2,4-D is an herbicide that was developed in the 1940s and is now manufactured by many chemical companies because the patent on it has expired. It was the first widely deployed herbicide used to control broadleaf plants and woody plants in small grain, fruit, nut, vegetable crops, pastures, and rangeland. 2,4-D can be found in many weed-control products and is often mixed with other herbicides. In 2014, the European Food Safety Authority published a peer review of the pesticide risk assessment of the active substance 2,4-D, concluding that "based on the available data, no chronic or acute concerns were identified for the consumers" (EFSA, 2014a, p. 1). EFSA and other regulatory agencies (e.g., US EPA, Canadian regulatory authorities) also do not consider 2,4-D to be a human carcinogen. On the contrary, in 2015, the IARC finalised a hazard classification of the herbicide 2,4-D and concluded that the substance should be classified as 'possibly carcinogenic to humans' (IARC, 2017a). In December 2015, the European Commission renewed the approval of 2,4-D as active substances for use in plant protection products.

3-isopropyl-1H-2,1,3-benzothiadiazin-4(3H)-one 2,2-dioxide, more commonly known as bentazone. Bentazone is manufactured by the BASF Corporation and its primary use is for large scale agriculture – particularly rice, beans, corn, and peppers. Concern for the use of this chemical is directed towards toxicity when it comes into contact with skin, potential harm from ingestion, and environmental concerns - mostly confined to groundwater. As an herbicide, bentazone has been subject to the review of many regulatory agencies or organisations dedicated to making risk assessments on its effects on human health and the environment. The European Commission had approved bentazone for use in the EU; however, the recent expiry of the authorisation in June 2017 prompted discussion in EU Member States as to whether extension should be warranted. EFSA and other agencies concluded that genotoxic, carcinogenic or neurotoxic effects are not produced by bentazone. However, EFSA together with other regulatory agencies in the EU have

identified several data gaps (in the mammalian toxicology area; in potential endocrine disrupting properties; risks to consumers; etc.) (EFSA, 2015a), which did not allow the finalisation of the risk assessment of bentazone. The European Commission has suggested to renew the EU authorisation of bentazone for the maximum period (until the 31st of January 2032). However, it requested further data confirming bentazone's safety. Similarly, the US Environmental Protection Agency (US EPA) has assumed the tasks of both assessing bentazone risks and directly regulating the substance in the United States. Currently, the US EPA is still conducting a risk assessment of bentazone, however, based on its preliminary scientific evaluations issued in 2014, it is highly likely that the licence of bentazone will be extended in the US.

Neonicotinoids are a new class of chemicals that are used as insecticides. Neonicotinoid pesticides target the central nervous system of insects, causing paralysis and death. They include imidacloprid, acetamiprid, clothianidin, dinotefuran, nithiazine, thiacloprid and thiamethoxam. Following the international controversy over potential links between neonicotinoids and the disappearance of bee colonies, several regulatory agencies have started to re-evaluate licensed neonicotinoids (imidacloprid, clothianidin, thiamethoxam) in their jurisdictions. In 2013, as per Commission mandate, EFSA conducted three peer reviews of the pesticide risk assessments of the active substances imidacloprid, clothianidin and thiamethoxam. EFSA reached the conclusion that the three neonicotinoid pesticides cause an acute risk to honey bees. Following the scientific conclusion of EFSA, the European Commission restricted the use of plant protection products containing three neonicotinoid active substances (i.e., clothianidin, imidacloprid and thiamethoxam) to protect European honeybees (Regulation (EU) No 485/2013). On the 28th of February 2018, EFSA updated its risk assessments of the three neonicotinoids – clothianidin, imidacloprid and thiamethoxam – concluding that, overall, the assessed neonicotinoid pesticides cause a high risk to honeybees, bumblebees and solitary bees. On the contrary, the use of the neonicotinoid pesticides is not restricted in the US and Canada because their regulatory agencies have arrived at different scientific conclusions than EFSA. The US Environmental Protection Agency claimed that honeybees are not exposed to the neonicotinoid pesticides to the extent that could cause an acute risk to them. Currently, the US EPA is re-assessing the risks of neonicotinoid pesticides to bees.

Chapter 3

I – Comparisons of the institutional design of (regulatory) agencies and bodies

The previous chapter has shown that one substance can be given different assessments by various bodies. For example, in 2015, the International Agency for Research on Cancer (IARC) suggested the existence of a probable carcinogenic link to glyphosate in humans, while numerous regulatory agencies, such as the European Food Safety Agency (EFSA), the European Chemicals Agency (ECHA) and the United States Environmental Protection Agency (US EPA) have also conducted risk assessments and arrived at different scientific conclusions. In a similar vein, regulatory bodies disagree on the risks and hazards caused by the herbicide 2,4-D and neonicotinoid pesticides. To explain the different conclusions at which agencies have arrived, this chapter first reviews the institutional designs of risk assessors in terms of their:

- Formal mandate and accountability mechanisms
- Independence and transparency policies
- Selection of scientific experts
- Procedures followed in the scientific assessments
- Internal/external control mechanisms

The respective agencies' institutional designs are introduced and discussed in detail, and include:

- European Union agencies: The European Food Safety Authority (EFSA) and the European Chemicals Agency (ECHA)
- National agencies: The Federal Institute for Risk Assessment (BfR)
- International bodies: The International Agency for Research on Cancer (IARC)
- Agencies outside the EU: The United States Environmental Protection Agency (US EPA)

The decision to cover the aforementioned agencies was motivated by the following: the study focusses on (1) the agencies that have produced scientific assessments at the EU-level or assisted EU agencies (e.g., the German regulatory authorities), (2) the agencies that arrived at different scientific conclusions compared to the EU agencies (the IARC (in the case of glyphosate) and the US EPA (in the case of neonicotinoid pesticides: imidacloprid, clothianidin and thiamethoxam). Such a case selection strategy assures the representation of relevant (regulatory) agencies worldwide: while the IARC is as a case of international bodies, the US EPA is a typical case of most relevant regulatory agencies operating outside of the EU (i.e., Australian, New Zealand and Canadian regulatory agencies have comparable institutional designs to the US EPA).

1. European agencies: EU and national regulatory bodies

European Food Safety Authority (EFSA)

Mandate and accountability mechanisms
Established in 2002 with the General Food Law (Regulation (EC) 178/2002), EFSA is the agency of the EU that provides independent scientific advice on food-related risks. EFSA is funded by the EU; however, it was created to work independently of the European legislative and executive institutions such as the European Commission, the Council, the European Parliament as well as Member States (Regulation (EC) 178/2002).

EFSA was created in the aftermath of major food crises in the late 1990s to ensure that robust and rigorous scientific advice and communication of risks are provided to EU institutions and Member States. As a result, the responsibility to deliver independent scientific outputs are regarded as one of the core pillars of EFSA day-to-day tasks as well as its overall mission. The General Food Law created a EU-level food safety system in which EFSA is exclusively in charge of the scientific aspects of food safety regulation, i.e. EFSA is responsible for risk assessments (science), whereas the European Commission together with other EU institutions take responsibility for risk management (i.e., policy). As the risk assessor, EFSA provides scientific opinions that lay the foundations for European legislation in the areas of plant protection, plant health, food and feed safety, nutrition and animal health and welfare. EFSA also has a duty to communicate its scientific findings to the public and interested stakeholders.

The Executive Director (currently Bernhard Url, appointed in 2014) and the Management Team are responsible for the day-to-day activities of EFSA (EFSA, 2018g). The Management Board of EFSA is mandated to act in the public interest. The Board has an important duty to ensure that EFSA operates efficiently and delivers its mandate in line with its founding regulations as well as takes into account the expectations of EU and Member State institutions, stakeholders and the public. The board consists of 15 members with wide-ranging expertise. It is important to note that the members of the board do not represent a Member State, government, organisation or particular sector. However, four members do represent the interests of consumers and other interests in the food industry. The European Commission is also represented. The board members are appointed by the Council of the European Union – in consultation with the European Parliament – based on a shortlist prepared by the Commission ensuing an open call for expressions of interest (see the General Food Law (Regulation (EC) 178/2002)).

The key tasks of the board are (1) to guarantee appropriate accountability and financial management, (2) to ensure that EFSA's activities follow its mandate and missions, (3) to plan EFSA's budget and work programmes as well as monitor their implementation, and (4) to appoint the Executive Director and members of the Scientific Committee and the Scientific Panel.

Independence policies

Independence (alongside scientific excellence, openness, innovation, cooperation) is one of the key values of EFSA: "EFSA is committed to safeguarding the independence of its experts, methods and data from any undue external influence and to ensuring that it has the necessary mechanisms in place to achieve this" (EFSA, 2018m; see also Regulation (EC) No 178/2002). Assuring independence is one of the core aims of EFSA, given that it was created as part of a broader legislative reform designed to re-establishing the confidence of EU citizens in the ability of the EU to guarantee safety of the food supply (Alemanno, 2016; Alemanno and Gabbi, 2016; Rimkutė, 2016). EFSA communicates that its independence policies ensure the impartiality of the persons participating in EFSA's operations. The founding regulation of EFSA (Regulation (EC) No 178/2002)) and secondary legislation require legal, financial and regulatory independence. They aim at preventing conflicts of interests by requiring the concerned actors to declare all interests held by them. They consider financial investments from business actors impacted directly or indirectly by EFSA's operations as one of the key sources of attention when it comes to potential conflicts of interests. EFSA has a system that is meant to prevent conflicts of interest of its external scientific experts and processes (see table below).[10]

"EFSA's existing range of safeguards rests on a comprehensive system for avoiding conflicts of interest among its external scientific experts. These measures include:
A multi-layered scrutiny system of annual declarations of interest (ADoIs), specific declarations of interest (SDoIs) and oral declarations of interest (ODoIs). ADoIs are submitted by all members of EFSA's Scientific Committee, Scientific Panels and Working Groups.
All DoIs are screened to identify potential conflicts related to an expert's professional activities and financial interests.
A range of options is available to resolve conflicts e.g. the expert may be considered ineligible for membership or chairmanship of a panel, or can be asked to relinquish a position, or shares in a company.
Compliance checks are performed on a sample of DoIs twice a year by staff members not involved in the assessment and validation process.
Regular external audits are carried out by the European Court of Auditors, the Internal Audit Service of the European Commission, and external contractors." (EFSA, 2017d).

EFSA communicates that it is committed to a "robust set of measures and working practices to safeguard the independence of its scientific work and avoid conflicts of interest" (EFSA, 2018i). However, the independence aspects of EFSA's conduct are regarded as controversial by many stakeholders. EFSA is often accused of having too close

[10] Please see the following documents for further information: EFSA, *Decision of the Executive Director of the European Food Safety Authority on Competing Interest Management*, 2017; EFSA, *EFSA's Policy on Independence*, 2017; EFSA, *Decision on Declarations of Interests*, 2012; EFSA, *EFSA report to the European Parliament on the implementation of its Independence Policy 2007-2012*, 2012; EFSA, *Decision concerning recovery orders related to staff missions*,2009; EFSA, *Guidelines on Gifts and Hospitality*,2012; EFSA, *Declarations of Interest*, Accessed: March 14, 2018; EFSA, *Independent science*, accessed: March 14, 2018

ties with industry and serious conflicts of interest: "Over half of the 209 scientists sitting on the agency's panels have direct or indirect ties with the industries they are meant to regulate. A much clearer and stricter independence policy needs to be set up and rigorously implemented to restore the Authority's reputation and integrity" (Horel and Corporate Europe Observatory, 2013, p. 1). Furthermore, more recently experts analysing EFSA's conflict of interest practices have discovered that 46% of current scientific experts contributing to EFSA panels have a financial conflict of interests, according to the Corporate Europe Observatory (Pigeon, 2017). In addition, EFSA currently faces new independence-related allegations as experts analysing EFSA's activities have noted that in the process of the renewal of the European Food Safety's Authority's Management Board, the candidates with conflicts of interests are being considered (Corporate Europe Observatory, 2018b).

EFSA receives criticism not only regarding the independence of its experts, but also the independence in its processes. In 2012, the European Court of Audits assessed policies and procedures for the management of conflict of interest situations for EFSA (European Court of Audits, 2012a).[11] The Court has discovered that EFSA does not managed the conflict of interest situations adequately. A number of deficiencies of varying degrees have been identified in EFSA policies and procedures as well as their implementation. Furthermore, in terms of the glyphosate risk assessment, the Corporate Europe Observatory (2017a) has published an investigatory article communicating that industry revised EFSA's Glyphosate scientific assessment ahead of its publication: "Shortly before the agency [EFSA] revealed its 2015 safety assessment for the world's most widely-used herbicide, industry representatives were asked to file redaction requests and were even able to edit the documents at the very last minute. EFSA argues this is normal practice" (Corporate Europe Observatory, 2017a). This implies that EFSA faces serious criticism regarding its de facto independence.

In response to the allegations, EFSA reiterates that it (as well as other regulatory agencies worldwide) is dependent on scientific information (studies) provided by the applicants (companies). As a result, according to EFSA, it is assumed by some stakeholder groups that this by default leads to the conflict of interest. In its statement addressing stakeholder concerns related to the EU assessment of glyphosate EFSA explained: "In the EU regulatory system for pesticides, the burden of proof of safety lies with the company that seeks to place their products on the market. This system is common to many regulated industries in the EU, including medicines. In practical terms, this means that applicants are required to present a dossier containing a set of mandatory guideline studies and to carry out a literature review of scientific papers published in the last 10 years, among other requirements. It is the role of Member State and EFSA experts to verify the applicant's proposals, which they do by evaluating the findings and raw data of the mandatory guideline studies and by appraising the studies in the open literature according to a set of uniform scientific principles. In this way, EU experts are able to reach their own conclusion about the safety of the active substance in question" (EFSA, 2017e).

[11] Please see the report here: European Court of Audits (2012b)

This statement was issued in the context of the 'Monsanto papers' that took place in the US, however also significantly influenced debates in the EU. In the EU context, the 'Monsanto papers' scandal refers to the Parliamentary hearing that took place on the 11th of October 2017 and was held by the European Parliament Committees ENNVI and AGRI (for more information please access the EP website). In this context, EFSA and its stakeholders discussed pertinent issues regarding the EU regulatory system, the role of EFSA in it and lessons learned from the US. Furthermore, such issues as independence, transparency and the role of science in risk assessments were touched upon.[12] In this context, the European Commission requested EFSA to explain what impact the allegations about Monsanto ghost-writing scientific review articles had on the overall EU assessment of glyphosate. EFSA responded by stating that: "Following this investigation, EFSA can confirm that even if the allegations regarding ghost-writing proved to be true, there would be no impact on the overall assessment as presented in the EFSA Conclusion on glyphosate" (see EFSA, 2017f, p.5). Furthermore, the European Parliament (the Environment (ENVI) and Agriculture (AGRI) Committees) organised a public hearing - "The Monsanto papers and glyphosate" – in which the issue of 'Monsanto papers' was addressed. The presentation of the representatives of agencies, scientific community and NGOs can be found on the European Parliament's website.

Overall, EFSA is responsive to the criticisms of its stakeholders regarding its independence-related weaknesses. To illustrate, EFSA has revised and improved its independence policies which resulted in the new Independence Policy (EFSA, 2017c). The document communicates that EFSA strives for "the impartiality of the persons participating in EFSA's operations based on the reassurance provided by projects securing the neutrality of the methods and data the Authority uses" (EFSA, 2017, p. 4). In particular, EFSA puts strong emphasis on its commitment to handling the conflict of interests in a rigorous manner: "Given the importance that experts' judgment has in EFSA's work, this policy [focusses] on the Authority's ability to ensure that professionals contributing to the work of EFSA perform their tasks in an impartial manner, without favour or discrimination. This presupposes, among other things, that these individuals are devoid of conflicts of interest (CoI) harmful to the Authority's work. This policy also outlines how EFSA prevents the occurrence of CoI" (EFSA, 2017c, p. 4). Furthermore, the most recent strategic document issued by EFSA emphasises that EFSA is committed to achieve the independence of its experts, methods and data from any external influence (EFSA, 2016a). See which novel aspects were integrated in the new independence policy in the table below.

[12] In the US, the scandal refers to the following allegations: "the Monsanto Papers show the company's [Monsanto's] real, and rather troubling, approach to science and evidence. Revelations include confirmation that the company hardly tested the real-world toxicity of its products, actively avoided pursuing studies which might show unwelcome results, and ghostwrote the studies of supposedly independent scientists. The documents also show Monsanto systematically attacked scientists whose research threatened their profits, as aptly summarised in a 2001 email by a Monsanto executive"(Corporate Europe Observatory, 2018).

"The revised policy now includes:
A new definition of what constitutes a conflict of interest, which brings EFSA into line with the most recent rules adopted by the European Commission for its expert committees.
A comprehensive set of "cooling-off" rules: external experts will be automatically barred from joining EFSA's scientific panels if in the preceding two years they have been employed by, acted as consultants to, or have offered scientific advice to organisations that work in areas covered by EFSA's remit. The cooling-off rules also apply to experts who have received research funding from such organisations over the same period.
A requirement that experts declare the proportion of their annual earnings received from any organisation, body or company whose activities fall within EFSA's areas of work. This information will be published and used as part of the DoI assessment.
Publication of the list of EFSA's partner organisations, such as national and international authorities, universities or research institutes.
Member State experts who take part in peer review meetings to be subject to the same scrutiny and transparency measures as panel experts" (EFSA, 2017d).

EFSA strongly reiterates its commitment to the new independence policies and its attempts to strive for improvements in its actual independent practices. This is reflected in their public communication. Jaana Husu-Kallio, Chair of the Board, noted: "The next challenge is to implement the policy, to turn the words into action. We will do this by the end of 2017 so that the new rules can be used in the renewal process for our scientific panels, which begin new terms in 2018." (EFSA, 2017d). However, a group of stakeholders who have scrutinised the changes in the new independence policy remain sceptical: "The new independence policy is a modest improvement compared to the previous one. It does not close the current policy's main loopholes, however. As a consequence, the improvements brought by this new policy (ban on consultancy contracts for, scientific advice to and managerial positions with regulated companies and organisations funded by them), while real, remain limited" (Corporate Europe Observatory, 2017c).

Transparency policies

Transparency and openness are essential aspects of EFSA's work and are integrated in its founding regulation (Regulation (EC) No 178/2002, articles 38 and 39) (see table below). EFSA emphasised that transparency (defined as "access to data, information and documents") and openness (i.e., engagement with stakeholders) have been the underlying values for EFSA since its inception. EFSA communicates that "openness and transparency mean that EFSA is able to meet the legitimate need of stakeholders to understand the basis for risk assessment" (EFSA, 2017d). For this purpose, EFSA is committed to making its scientific opinions, the agendas and minutes of meetings and other key documents publicly available. Furthermore, more recently, EFSA started to broadcast important meetings and events through its website. In addition, EFSA regularly opens meetings of its Scientific Committee and Panels to observers.

The founding regulation of EFSA specifies in Article 38 as follows. EFSA should make public without delay, in particular:
"(a) agendas and minutes of the Scientific Committee and Panels;
(b) the opinions of the Scientific Committee and Panels immediately after adoption, including minority opinions (if any);
(c) the information on which opinions are based;
(d) the annual declarations of interest made by selected people participating in its work;
(e) the results of its studies;
(f) the annual report of its activities; and
(g) requests from the European Commission, the European Parliament or a Member State for scientific opinions which have been refused or modified and the underlying justifications" (Regulation (EC) No 178/2002, p. 18-19).

EFSA organised several activities that were aimed to contribute to generating more transparent and open scientific assessments that would be in accordance with the recent discussion paper on transformation to an "Open EFSA" (EFSA, 2014b) in order to deliberate on how EFSA can achieve two strategic goals within the next five years: "(1) to improve the overall quality of available information and data used for its outputs and (2) to comply with normative and societal expectations of openness" (EFSA, 2015h, p. 3). Furthermore, it is evident from the public communication and activities of EFSA that it spends much effort to advance transparency related aspects of its day-to-day activities. This can be observed by the number and extent of activities dedicated to transparency related issues.[13]

However, when it comes to the day-to-day activities of EFSA, a group of stakeholders have pointed out that there is much room for improvement regarding the actual transparency practices of EFSA, as well as how the regulatory systems regarding pesticide peer reviews works. EFSA and the BfR were accused of serious transparency flaws in the scientific evaluation process. For instance, the scientific community expressed strong criticism towards EFSA: "we urge you [EFSA] and the European Commission to disregard the flawed EFSA finding on glyphosate in your formulation of glyphosate health and environmental policy for Europe and to call for a transparent, open and credible review of the scientific literature" (Portier et al. 2015, p. 2). In response to the criticism and an increased public interest in the glyphosate issue, the raw data that EFSA relied on in its risk assessment (i.e. all the genotoxicity and carcinogenicity studies used in the glyphosate assessment) has been published by EFSA, meaning that the conclusions could be

[13] Please see the following EFSA documents for more information: Implementing measures of transparency and confidentiality requirements ; Openness, transparency and confidentiality - general principles; Decision concerning access to documents; Mandate for a new policy on information accesS; Editorial: Increasing robustness, transparency and openness of scientific assessments; Outcome of the targeted consultation of the EFSA Journal editorial on increasing openness, robustness and transparency of scientific assessments.

independently scrutinised and reanalysed by the interested scientists (EFSA, 2016c). This led to more heated debates because Prof. Portier reanalysed the data released upon request and found that EFSA and ECHA omitted relevant data in their assessments: "eight instances where significant increases in tumor response following glyphosate exposure were not included in the assessment by either EFSA or ECHA. This suggests that the evaluations applied to the glyphosate data are scientifically flawed, and any decisions derived from these evaluations will fail to protect public health" (Portier, 2017, p. 1).

In the case of glyphosate, according to the interviewed EFSA representatives, EFSA did its utmost to meet the expectations and requests of information coming from various stakeholders (EFSA representative #2). For instance, EFSA emphasises that it "has gone to great lengths to be open and transparent about the EU assessment of glyphosate. It has published its final Conclusion and 6,000 pages of background documents, which include the comments and views of experts offered during the process as well as very detailed information about how EU experts appraised each and every study and how they evaluated the evidence" (EFSA, 2017e, p. 4-5). The published documents can be accessed on EFSA website (see EFSA, 2015f).

Furthermore, in response to Public Access to Document requests, EFSA has released the findings and raw data from all the genotoxicity and carcinogenicity studies that were tendered by industry regarding glyphosate. The Authority notes that "in doing so, EFSA rejected the vast majority of confidentiality claims submitted by industry and provided the requestors with enough information to allow full independent scrutiny of the EU assessment" (EFSA, 2017e, p. 5). EFSA marked that such transparency practices are highly exceptional: "As far as EFSA is aware, it is the first regulatory body anywhere in the world to release this amount of information related to pesticide risk assessments" (EFSA, 2017e, p. 5; see also EFSA, 2016d). However, transparency-related issues and accusations reoccur. To give an example, in 2013, two groups of stakeholders – ClientEarth and Pesticide Action Network Europe (PAN Europe) – accused EFSA for refusal to access to relevant documents (see more on the background to the dispute here: (Judgement of the Court, 2015). The court decided to annul the decision of EFSA of the 12th of December 2011.[14] This court case illustrates that stakeholders are concerned about EFSA's transparency practices and it

[14] "On 12 December 2011 EFSA adopted and informed ClientEarth and PAN Europe of a further decision on the application which they had submitted on 23 December 2010. EFSA stated that it had decided to 'withdraw', 'annul' and 'replace' its decision of 10 February 2011. In that further decision, EFSA granted ClientEarth and PAN Europe access to, inter alia, the individual comments of the PPR and PSC external experts on the draft guidance document. EFSA stated however that it had redacted the names of those experts, pursuant to Article 4(1)(b) of Regulation No 1049/2001 and EU legislation on the protection of personal data, in particular Regulation No 45/2001. EFSA stated in that regard that the disclosure of the names of those experts was a transfer of personal data, within the meaning of Article 8 of Regulation No 45/2001, and that the conditions for such a personal data transfer laid down in that article were not fulfilled in this case." (Judgement of the Court, 2015)

takes much time and effort for them to obtain information that they have the right to request.

The interviewed representative of EFSA, however, noted that to meet the concerns of the public and stakeholders in relation to glyphosate, EFSA spent much time and effort to release much information about the glyphosate risk assessment (i.e., content) as well as peer-review process followed by EFSA and Member States for the renewal of the approval of the pesticide active substance (i.e., procedures followed) (EFSA representative #2).

However, major concerns regarding EFSA transparency and independence remains prominent. For instance, the scientific conclusions and processes through which EFSA and the BfR conclusions were reached have received much criticisms from representatives of the scientific community. In particular, there were concerns about EFSA and the BfR transparency and independence practices that according to them are less advanced compared to the IARC which leads to the less credible scientific conclusions (see table below).

Open letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR

"We reviewed these two differing decisions on the human carcinogenicity of glyphosate and conclude that the IARC WG decision is by far the more credible. The IARC WG decision was reached relying on open and transparent procedures by independent scientists who completed thorough conflict-of-interest statements and were not affiliated or financially supported in any way by the chemical manufacturing industry. It is fully referenced and depends entirely on reports published in the open, peer-reviewed biomedical literature. It is part of a long tradition of deeply researched and highly credible reports on the carcinogenicity of hundreds of chemicals issued over the past four decades by IARC and used today by international agencies and regulatory bodies around the world as a basis for risk assessment, regulation and public health policy.

In contrast, the BfR decision is not credible because it is not supported by the evidence and it was not reached in an open and transparent manner.

Accordingly, we urge you and the European Commission to disregard the flawed EFSA finding on glyphosate in your formulation of glyphosate health and environmental policy for Europe and to call for a transparent, open and credible review of the scientific literature." (Portier et al., 2015, p.2)

EFSA responded to the open letter by stating that it strongly disagrees with these accusations (EFSA, 2016b, see p. 3). EFSA outlined which transparency practices were followed and how open EFSA was regarding, in particular, the case of glyphosate.

Regardless of EFSA's efforts to be transparent about procedures followed and studies used in the case of glyphosate scientific evaluation, various stakeholder groups have raised concerns about transparency of EFSA and EU risk assessment system. For instance, on the 6th of October 2017, the European Commission received the submission of 'Stop

Glyphosate' European Citizens' Initiative. More than 1 million EU citizens have requested the Commission "to propose to Member States a ban on glyphosate, *to reform the pesticide approval procedure,* and to set EU-wide mandatory reduction targets for pesticide use" (European Commission, 2017a). The initiative required the EU scientific evaluation of pesticides to be based on exclusively on published studies: "The Commission must ensure that the scientific evaluation of pesticides for EU regulatory approval is only based on published scientific evidence, which is commissioned by competent public authorities instead of the pesticide industry. Regulatory studies should be published in full and open to scientific scrutiny. The potential for conflicts of interest should be eliminated, by disconnecting contracting laboratories' finances from the commissioning procedure, and by prohibiting pesticide producers from choosing which authority they charge and pay for the authorisation procedure." (Corporate Europe Observatory, 2017d).

The Commission adopted a communication the 12th of December 2017 setting out the actions it intends to take in response to the initiative. After considering the initiative, the Commission reached the following conclusions: (1) "*there are neither scientific nor legal grounds to justify a ban of glyphosate*, and the Commission will not make a legislative proposal", (2) the Commission plans "to come forward with a legislative proposal by May 2018 to enhance *the transparency in scientific assessments and the quality and independence of the scientific studies that are the basis of the assessments carried out by the European Food Safety Authority (EFSA). The proposal will also cover other aspects, such as the governance of EFSA"*; (3) the Commission intends to "focus on the implementation of the Sustainable Use Directive, and will re-evaluate the situation, initially in a report to Council and the Parliament on the implementation of the Directive to be produced in 2019" (European Commission, 2017b).

On the 11th of April, the Commission issued a proposal on transparency and sustainability of the EU risk assessment model in the food chain (European Commission, 2018b). The proposal was a direct response to the European Citizens Initiative on glyphosate. It stipulates to EU citizens' concerns regarding the scientific evaluations on glyphosate risks. To address these concerns, the Commission intends to strengthen the transparency in the risk assessment process. The Commission also intends to provide supplementary guarantees of reliability, objectivity and independence of the studies used by EFSA in risk assessments. Furthermore, the proposal communicates that the Commission is committed to "Better Regulation", i.e. "the need to improve the transparency in the EU decision-making cycle as well as the need to safeguard European Food Safety Authority ability to get access to a sufficiently high number of qualified and multidisciplinary scientific experts. An important element is also the need to reinforce the co-operation between EFSA and national scientific bodies, increasing Member States' involvement in EFSA's operation" (European Commission, 2018b).

Selection of scientific experts

EFSA states that "the knowledge, experience and decision-making of EFSA's scientific experts are at the heart of our work" (EFSA, 2018l). Authority's Scientific Panels of experts are responsible for the EFSA's scientific risk assessments, while the Scientific Committee has the task of assisting and supporting the work of the Panels on scientific issues. In particular, the committee concentrates on developing harmonised risk assessment

methodologies. EFSA staff are in charge of supporting the Scientific Panels and Scientific Committee in conducting EFSA's scientific work.

EFSA communicates that its Scientific Committees and Panels consist of independent scientific experts with a three-year mandate. The Declarations of Interests and CVs of the PPR (Panel on Plant Protection Products and their Residues) Panel Members (2015-2018) are publicly available. To elaborate, EFSA launches a call for expression of interest from experts who will be potentially engaged in the risk assessment process of the substance. Applications are considered from both the European Union (EU) and the rest of the world. EFSA selects experts for a Panel or the Committee based on selection criteria such as risk assessment experience and expertise in peer reviewing scientific work, with external evaluators ensuring the fairness of the selection process (EFSA, 2017b). All applicants must complete an Annual Declaration of Interests (ADoI), which is evaluated by EFSA for potential conflicts of interests. A second screening of ADoIs is also completed before nominated candidates are invited to their first meeting (EFSA, 2017b).

EFSA clearly specifies how scientific experts are selected and what the core selection criterion are.[15] In selecting its experts, EFSA pays attention to the following factors: (1) The expertise required (i.e., "specific scientific expertise and experience; additional expertise and potential contribution to a diverse range of scientific disciplines in the process of opinion development; and the overall mix of knowledge areas available to the Scientific Panel/ Committee to cover its foreseen needs" (EFSA, 2017b, p. 6); (2) Nationality balance among Member States; (3) Gender balance (among equally qualified candidates, preference shall be given to those belonging to the underrepresented gender). In addition, all scientific experts working for EFSA are required to sign declarations of interests, declarations of commitment, including a commitment to act independently (EFSA, 2017).

However, when it comes to the day-to-day activities of EFSA, some stakeholders note that there are several loopholes when it comes to the declarations of interests in the pesticide peer reviews processes and the representatives coming from the Member States: "80 per cent of national experts who took part in the peer review of the European Food Safety Authority's (EFSA) assessment have refused to be identified, making it impossible to know whether the authors of the EU risk assessment were independent from relevant economic and political interests, or in fact had conflicts of interest" (Corporate Europe Observatory, 2017b).

Procedures

In the EU, before a pesticide can be authorised for use, the safety of its active substance must be assessed. EFSA follows the following key steps in the process (see document: who assesses pesticides in the EU; the table below summarises the formal procedure in accordance with Article 12 of Regulation (EC) No 1107/2009):

[15] see Decision of the Executive Director concerning the selection of members of the Scientific Committee the Scientific Panels, and the selection of external experts to assist EFSA with its scientific work

1. Application submitted: Application for approval of active substance submitted to an EU Rapporteur Member State (RMS);
2. Application verified: RMS verifies that the application is admissible;
3. Report prepared: RMS prepares a Draft Assessment Report or Renewal Assessment Report that includes a risk assessment
4. Peer review: RMS shares report with EFSA, Member States and the European Commission. EFSA begins review of RMS report
5. Member State consultation: EFSA organises consultation with experts from Member States
6. Public consultation: EFSA canvasses stakeholders and any other interested parties for views on the report
7. Additional information: EFSA requests additional information from the RMS if needed
8. Report updated: Assessment report is updated by the RMS
9. EFSA issues conclusions: EFSA holds final consultation with experts from 28 Member States before issuing its conclusions
10. Draft decision: Committee comprising representatives of Member States votes on draft decision proposed by European Commission
11. Substance approved/rejected: Commission decides whether to allow the active substance to be used in pesticides in the EU. Member States can then decide whether pesticide products containing the substance should be authorised for use in their countries. (Source: EFSA, 2016f)

The interviewed EFSA representative emphasises an important role of Member States and their experts in the process of EFSA risk assessments: "What you see in the legislation concerning pesticides is that the first assessment is conducted by the rapporteur member state. EFSA's responsibility is, in cooperation with all other EU Member States, to revise the assessment that has been conducted by the rapporteur member state, and then to publish the conclusions. The legislation states that EFSA should cooperate with the Member States but does not specify how this consultation should be done. We have elaborated a process we call the peer review, focussing on the review of the science. As you know, peer review is one of the key elements in scientific assessment, and we have implemented this peer review process for the assessment of the pesticides. The aim of the peer review process is to check the assessment that has been conducted by the rapporteur member state. So, the first assessment is conducted by the rapporteur member state, but then the idea is to check this.

This has two aims: Obviously, we want to make sure that the assessment is correct, and in all cases, we see significant improvements in the assessment; and also, to be sure on the consistency and coherence for the whole assessment on pesticides. It is important for industry, but also for citizens that the quality of the assessment does not depend on the expertise of one particular Member State. All assessments should be the same, independent of who is the rapporteur Member State; and we ensure this through the peer review process. It is conducted by scientists in EFSA, and scientists in all Member States; and it is conducted for different scientific disciplines. We have personal consultations, so we collect comments; we define the key elements to be discussed; we organise expert meetings – tele-meetings or physical meetings, depending on the number of questions to be discussed and

their complexity – and following all this, the rapporteur Member State modifies their assessment, including all the comments from experts from EFSA, and publish a conclusion with a final recommendation for the European Commission." *EFSA representative #2*

In a nutshell, the EFSA conclusions on pesticides have a complex structure and are designed to assist the European Commission in its risk management decisions on the approval/renewal of approval of substances as well as Member States in the assessment and risk management decision on Plant Protection Products containing approved substances; furthermore, EFSA's conclusion support the review of the Maximum Residue Levels (MRLs) of pesticides. Please consult the figures below (see Figure 2; Figure 3; Figure 4; Figure 5) to learn about the common procedures regarding the renewal of approval of active substances under Regulation EU 844/2012.

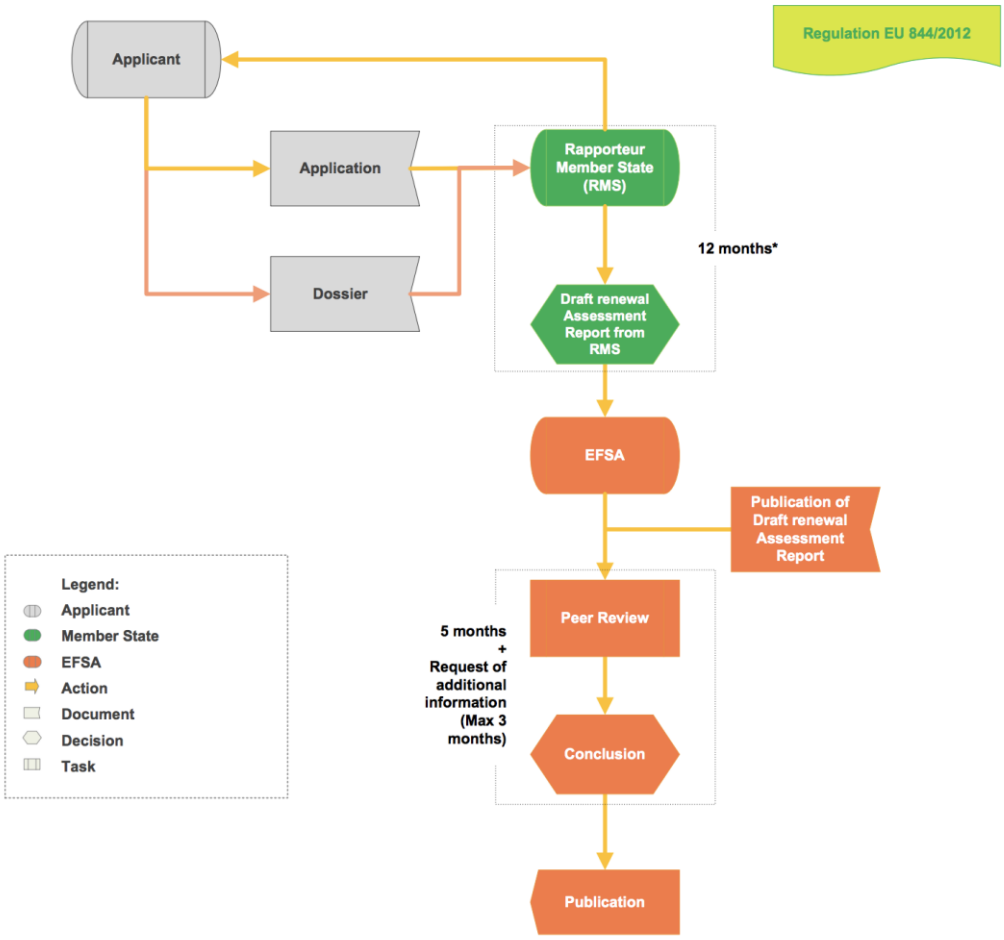

Figure 2. Renewal of approval under AIR programme: application procedure
Source: EFSA, *Applications helpdesk – Renewal of approval under AIR programme: application procedure*

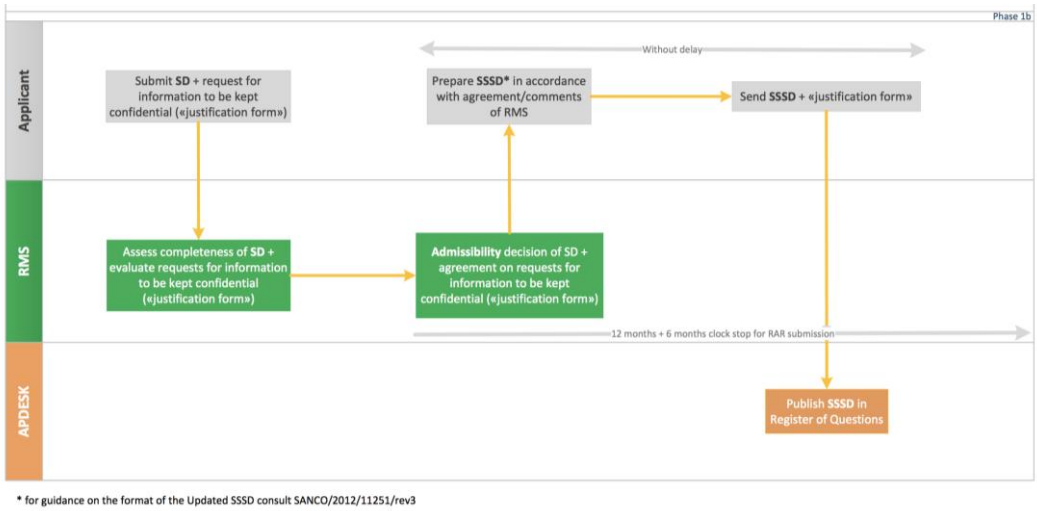

Figure 3. *Phase 2b Renewal of approval of active substances under Regulation EU 844/2012*. Source: EFSA

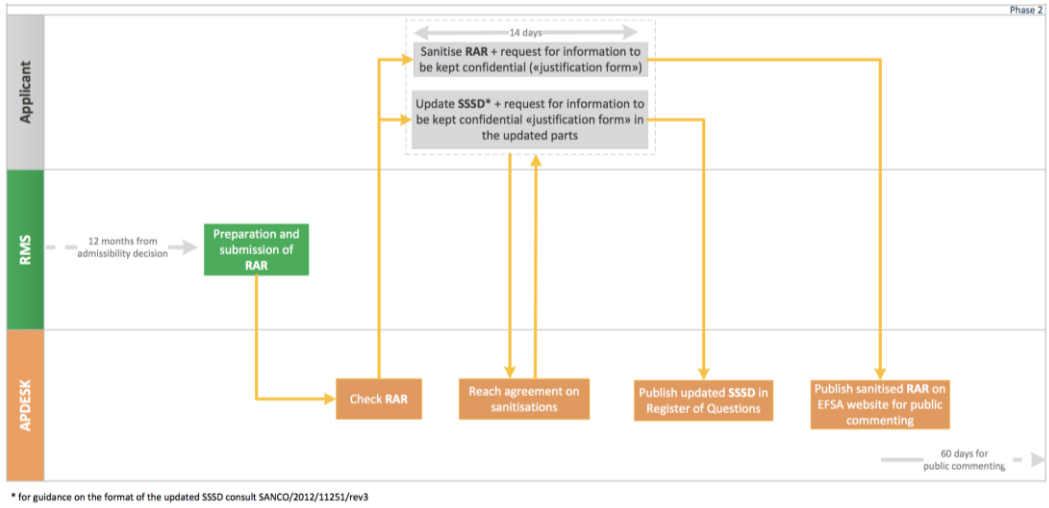

Figure 4. Phase 2: *RAR dispatch and call for comments*. Source: EFSA

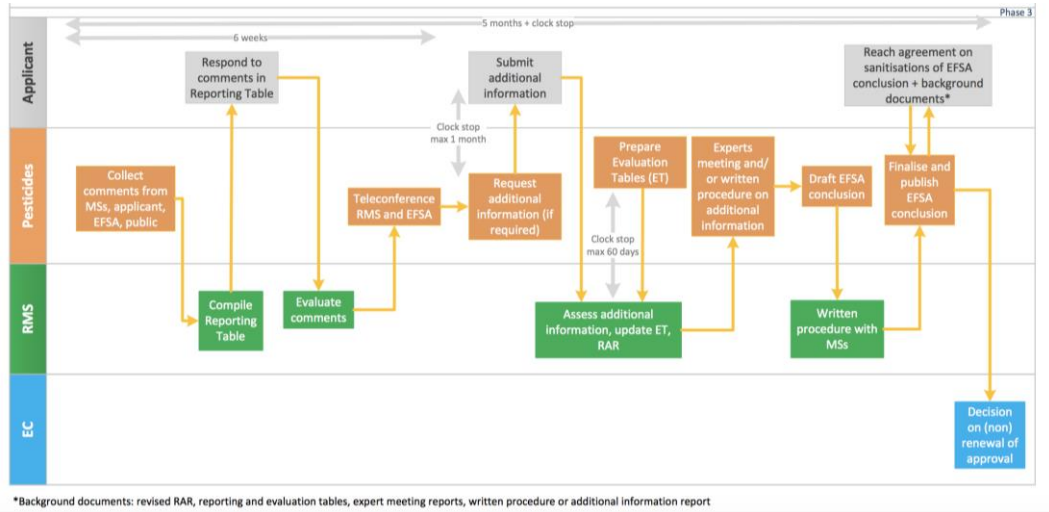

Figure 5. *Phase 3: EFSA Conclusions*. Source: EFSA

In the cases of glyphosate; 2,4-D; bentazone and neonicotinoid pesticides, EFSA followed all steps indicated above. The interviewed EFSA representative emphasised that EFSA is committed to following due processes specified in regulations defining EFSA tasks and responsibilities (EFSA representative #2).

Internal/external control mechanisms

In recent years, EFSA has worked on setting up and improving its Quality Management System (QMS) to guarantee a firm basis for scientific excellence, openness, independence, innovation and cooperation (EFSA, 2017a). QMS aims at guaranteeing that the quality of EFSA's scientific work is appropriately monitored and, when needed, strengthened: this contains self-review and customer feedback systems, which guarantees that scientific processes are developed consistently. Reviews and inspections are conducted by an internal auditor who reports to the EFSA's Management Board's Audit Committee, which, in turn, advises senior management on possible improvements to EFSA scientific work practices.

In terms of external evaluation, EFSA's Founding Regulation obligates EFSA to commission independent external evaluations of its activities and working practices. Relying on these evaluations, the Management Board makes suggestions on the future management plans and strategies of EFSA (EFSA, 2018h).

The analysis of primary documents and the interview with EFSA representative suggest that EFSA followed the standard procedures and policies in their glyphosate, 2,4-D, bentazone and neonicotinoid pesticides scientific evaluations. Even though EFSA received much criticism from various groups of stakeholders (and the European Court of Auditors) regarding its independence and transparency policies, it was responsive to this criticism by publicly defended its practices and altering its independence and transparency policies.

European Chemicals Agency (ECHA)

Mandate and accountability mechanisms

The European Chemicals Agency (ECHA) presents itself and its mandate as "the driving force among regulatory authorities in implementing the EU's ground-breaking chemicals legislation for the benefit of human health and the environment as well as for innovation and competitiveness" (ECHA, 2018a). ECHA core duties in terms of active substances are laid out in the Classification, Labelling and Packaging (CLP) Regulation ((EC) No 1272/2008) which is based on the United Nations' Globally Harmonised System (GHS). The regulation aims to guarantee a high level of protection of health and the environment and a free movement of substances, mixtures and articles.

The Management Board is the core governing body of ECHA (ECHA, 2018e). It has a supervisory role with general duty to manage (1) budgetary and planning matters; (2) the appointment of the Executive Director, (3) the members and the Chair of the Board of Appeal and the reporting of ECHA's activities to EU institutions. The Board consists of 28 members from Member States, six representatives of the European Commission, and two

representatives of the European Parliament. The key tasks of the board are to guarantee appropriate accountability.

Independence policies
Independence is one of the core values of ECHA: "We are independent from all external interests and impartial in our decision making. We consult members of the public openly before taking many of our decisions" (ECHA, 2018h). ECHA assures independence "by having transparent declarations of interest and taking measures to ensure that interests cannot have an impact on decision making in the Agency. In reality, that implies striking a delicate balance between having staff members with expertise and experience and, at the same time, strictly avoiding potential conflicts of interest" (ECHA, 2018h). According to ECHA's policy[16], a conflict of interest could occur in situations where the impartiality and objectivity of a decision is affected by the interest of an individual working in or with the Agency. As a result, personnel working for ECHA have to fill an annual declaration of interests. Furthermore, ECHA has a Conflicts of Interest Advisory Committee to support the Agency's Executive Director in ensuring independence of decision making.

In the context of the glyphosate scientific evaluation, ECHA received criticism from the Greenpeace European Unit regarding the independence and transparency of the European Chemicals Agency's Risk Assessment Committee (RAC). Stakeholders claimed that, in the case of glyphosate, "several members as well as the Chair of the Risk Assessment Committee appear to have a conflict of interest, according to ECHA's own criteria. […] By these standards, RAC members Slawomir Czerczak and Tiina Santonen appear to have conflicts of interest. Both are employed by public scientific institutes that also generate income from providing risk assessment consultancy services to the chemical industry" (Riss, Greenpeace European Unit, 2017, p.1-2).

ECHA defended its commitment to independence by issuing an open response letter to the concerned stakeholders: "your fundamental concern is whether this could call into question the impartiality of the impending opinion on glyphosate. Our answer is absolutely not. The chair and two members have not declared an interest in the substance and we believe this to be correct. Furthermore, in the development of any RAC opinion — including glyphosate – there is a very small group of active RAC members who on the one hand, do the analysis and draft the opinion and on the other, act as peer reviewers. The members you cite have not been involved in the analysis of data on glyphosate, nor in the drafting of the opinion, nor in peer-reviewing it. Rather they are two from 53 scientists who will discuss the opinion thoroughly and aim to reach consensus on the classification of glyphosate. All of them are independent in their judgement, all of them nominated by their respective governments and all of them appointed by our Management Board to undertake this important role. As a matter of interest, we will be publishing the names of the rapporteurs after the opinion has been agreed — we do not do it before, precisely so as to protect them from any lobbying" (Geert Dancet 7 March 2017).

[16] See ECHA's procedures and policies on independence: ECHA Policy for Managing potential Conflicts of Interest; Guidance for filling in the declaration of interest ; Guidance for the prevention of potential conflicts of interest in ECHA networks and expert groups

There were several exchanges of open letters between ECHA and the Greenpeace European Unit (see second letter of the Greenpeace European Unit (2017) and ECHA response (2017)). ECHA used this open exchange to emphasise its significant progress in its independence and transparency policies and practices. For instance, in 2012, the European Court of Audits issued a report on the management of conflict of interest in selected EU Agencies. The Court concluded: "The Court evaluated policies and procedures for the management of conflict of interest situations for four selected Agencies making vital decisions affecting the safety and health of consumers, namely the European Aviation Safety Agency (EASA), European Chemicals Agency (ECHA), European Food Safety Agency (EFSA) and the European Medicines Agency (EMA). The Court found that none of the selected Agencies adequately managed the conflict of interest situations. A number of shortcomings of varying degrees have been identified in Agency-specific policies and procedures as well as their implementation"(European Court of Audits, 2012a).[17] In its response letter to the Greenpeace European Unit, ECHA mentioned its progress in terms of criticism received from the European Court of Audits: "ECHA's independence policy builds on international best practice, as reflected in guidelines from the Organisation for Economic Co-operation and Development and the European Commission. The common objective of these is to protect the independence of public bodies whilst enabling them to collaborate with the best available experts. The European Court of Auditors audited ECHA's policy and procedures in 2015 and found that we had implemented all their recommendations from the 2012 special report on conflicts of interest. We are clearly in line with international best practice" (Geert Dancet 10 March 2017, p.1).

Transparency policies

Transparency is one of the core values of ECHA: "We are open and transparent in our actions and decision-making. We are easy to understand and to approach" (ECHA, 2018h). ECHA communicates that it aims to provide interested parties the opportunity to question, challenge and hold ECHA to account. ECHA's approach to transparency relies on three main pillars: (1) clear and transparent procedures; (2) open decision making; (3) information available.[18]

Please see the discussion above (i.e. independence policies) regarding the criticism about ECHA's transparency (and independence) policies and practices.

Selection of scientific experts

Within ECHA, the Committee for Risk Assessment (RAC) is responsible for providing scientific opinions on substances. Every Member State is allowed to nominate candidates for RAC. Those nominees are then made public on the ECHA website and appointed by the Management Board. Each Member State is allowed a maximum of two representatives per committee. At the moment, RAC has a total of 52 members (ECHA, 2015). The members of RAC are appointed for a three-year period. On their website, ECHA publishes all members of the committee including their CV and a Declaration of Interest. The Declaration of Interest states prior research interests, employment, funding and sponsors

[17] Please see the report here: European Court of Audits (2012b)

[18]For more information see: ECHA, 2014

of the members which helps ensuring transparency. It also reduces conflict of interests of the members, with the aim of ensuring an independent risk assessment by the Committee.

Procedures
Within ECHA, the Committee for Risk Assessment (RAC) is responsible for providing an opinion on substances that pose a potential risk to human health and the environment. The opinion of RAC is then forwarded to the European Commission. Their final opinion is based on the harmonised classification and labelling of substances (see Regulation ((EC) No 1272/2008).[19]

The Classification, Labelling and Packaging (CLP) legislation is legally binding in all Member States and directly applicable to all industrial sectors. "It requires manufacturers, importers or downstream users of substances or mixtures to classify, label and package their hazardous chemicals appropriately before placing them on the market" (ECHA, 2018g). One of the main aims of CLP is to determine whether a substance exhibits the properties that lead to a hazardous classification.

CLP criteria sets general packaging standards to ensure the safe supply of hazardous substances and mixtures. "In addition to the communication of hazards through labelling requirements, CLP is also the basis for many legislative provisions on the risk management of chemicals" (ECHA, 2018g). See the table and Figure 6 for more detailed information on how the process of harmonised classification and labelling unfolds in the EU system.

Harmonised classification and labelling (CLH)
"Manufacturers, importers or downstream users have to (self)-classify and label hazardous substances and mixtures to ensure a high level of protection of human health and the environment.
For hazards of highest concern (carcinogenicity, mutagenicity, reproductive toxicity (CMR) and respiratory sensitisers) and for other substances on a case-by-case basis, classification and labelling should be harmonised throughout the EU to ensure an adequate risk management. This is done through harmonised classification and labelling (CLH).
Harmonised classifications are listed in Annex VI to the CLP Regulation and should be applied by all manufacturers, importers or downstream users of such substances and of mixtures containing such substances.
CLH can be proposed for substances without a current entry in Annex VI to CLP, or to those with an existing harmonised classification, which would need to be changed either due to availability of new information, new scientific or technical developments, changes in the classification criteria or based on the re-evaluation of existing data.

[19] The Classification, Labelling and Packaging (CLP) Regulation ((EC) No 1272/2008) relies on the United Nations' Globally Harmonised System (GHS) and its aim is to guarantee a high level of protection of health and the environment, as well as the free movement of substances, mixtures and articles.

A Member State competent authority (MSCA), or a manufacturer, importer and downstream user of a substance can submit a CLH proposal to ECHA" (ECHA, 2018c).

ECHA can start the process of harmonised classification and labelling (CLH) when a Member State competent authority submits a proposal. The proposal must have sufficient evidence that the amount and usage of the substance is relevant to be assessed. In the case of glyphosate, the German agency – the Federal Institute for Occupational Safety and Health Federal Office for Chemicals (BAuA) – was the dossier submitter in May 2016 (ECHA, 2018c). Following this proposal, a 45-day long period begins during which a public consultation takes place. In the case of glyphosate, this period started on 2 June 2016 and ended on 18 July 2016 (ECHA, 2017). These consultations can be of any scientific nature regarding the classification proposal, as well as other potential risks associated with the substance. Following the end of the public consultation period, all non-confidential documents taken into account by ECHA were made available for the general public on the ECHA website. The dossier submitter then has the chance to respond to the submitted comments. Afterwards, RAC forms a draft opinion on the classification and labelling of the substance.

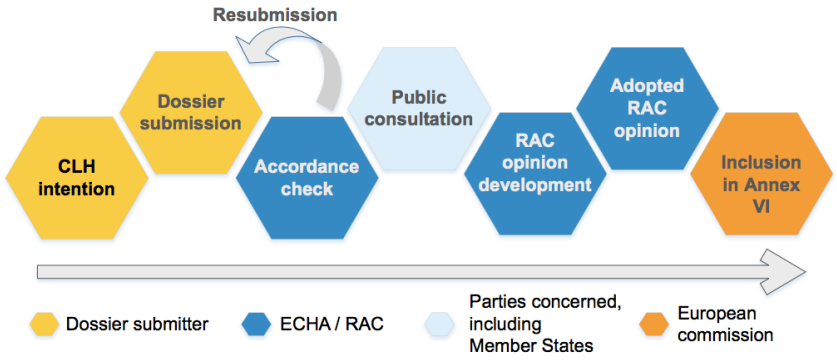

Figure 6. Steps of the harmonised classification and labelling (CLH) process

Table 3. Formation of final opinion by RAC

1	Day 1	Comments by the applicant on the draft opinion are distributed to RAC
2	Week 4	Draft of final RAC opinion
3	Weeks 4-6	Written comments and editing of final opinion
4	Week 6	Second revision period
5	Weeks 8-9	Discussion period, plenary and written editing building up the final opinion. Within the next 15 days, the secretariat will send out the final opinion of RAC and publication of all relevant documents.

Source: ECHA, 2014

The interviewed representative of ECHA further clarified how the steps of the harmonised classification and labelling (CLH) process unfold and how two EU agencies – EFSA and ECHA – interact and complement each other. The interviewed ECHA representative notes

that, normally, EFSA and ECHA work in parallel (especially when it comes to approval of new substances), however, at times the work of EFSA and ECHA follow each other, as clarified by the ECHA expert in the interview (see table below).

ECHA representative #1
"We [ECHA] are responsible for the regulation classification and labelling, where the agency provides an opinion on proposals for [harmonised] classification. This includes [harmonised] classification for pesticides. And that is where the two regulatory agencies [EFSA and ECHA] come together.

Now the process is as follows: The normal approval of pesticides' active ingredients goes through the pesticide regulation [Regulation (EC) No 1107/2009]; it involves the Member States, it involves EFSA. As part of that dossier they also provide a view on the hazard of the substance, but at that point in time they do not take a formal view on hazard classification. Because that formal view falls under the CLP regulation. But what's normally done is, as part of the dossiers which the Member States provide to EFSA, they also take a look at the hazard, because they need to know the hazard and the risk assessment. Therefore, very often at that point in time they already take a view on the hazard properties of the chemical; and we try to have a system where, preferably in parallel to the approval process under the pesticide regulation, the Member States also submit a dossier under the CLP regulation. So that the formal hazard classification is taken care of through that CLP process, in parallel to the risk assessment process under the pesticide regulation. We then provide an opinion on the classification which goes more or less in parallel to the risk assessment; and then the Commission can take its final view on the approval of the pesticide active ingredient knowing what the conclusion is of the hazard site in terms of classification. That's the ideal situation.

Now what happens very often in practice is, because we very often deal with substances which are already on the market, where the process has not been followed perfectly in the past, very often the reports which the member states submit to EFSA, this practice of having a parallel report on the classification labelling process, is not always happening. Quite often, there are delays; in some cases, Member States do not even submit the dossier at all. Therefore, we sometimes have a problem in matching the two regulatory processes."

Furthermore, the ECHA representative explained the process which unfolded in the case of glyphosate scientific evaluations:

ECHA representative #1
"In the case of glyphosate, it was indeed also the case that the Member States' authorities – the German authorities – first submitted the dossier on the risk assessment for re-approval to EFSA. It went through the discussion in EFSA, and whilst it was more or less [finalised], the IARC opinion came in, which started the whole

discussion on the carcinogenicity of glyphosate. When that happened, the decision-making process in EFSA was already quite far advanced, but there was not yet a formal proposal for classification provided to us; the CLP process hadn't started yet. The political discussions then started in reaction to the IARC discussions. EFSA then had already indicated in its draft final conclusion document and risk assessment that they did not consider glyphosate to be carcinogenic; this was based on the proposal from the German authorities. This discussion was taken further to their expert groups, which also concluded that there was no problem with glyphosate. Nevertheless, when the Commission took note of all these discussions, and the political debate was becoming more intense, then the Commissioner indicated that he did not want only the EFSA opinion without having a formal view from ECHA on the hazard classification; because there would be only one body providing a formal opinion on the hazard classification. That is when the temporary re-approval of glyphosate took place last year, with a clear request to Germany to submit the classification proposal as quickly as possible; they did so over the summer last year. Then, the CLP process here at ECHA started. We were asked to provide an opinion as quickly as possible; of course, we needed to follow the whole process and hold public consultation. Then we started to work and provided the opinion earlier this year. The opinion went back to the Commission, which concluded on the basis of the proposal that the substance should be reapproved."

It is important to note that in the case of ECHA procedures followed in the glyphosate case, the ECHA representative confirmed that all standard procedures had been followed, however, as was the case with other agencies – e.g. EFSA and BfR – ECHA spent much time and effort to communicate its conclusions and procedures: "The process which we have followed for glyphosate is not unique in terms of which steps were taken. We have done 250 hazard classifications in the last decade, and we followed the normal process. The only point which was unique is that, given that there was so much political tension, we paid more attention to being very extensive in our communication. We wrote Q&As, we put a lot of information on our website, which is not normal for every case. We had enormous numbers of press questions and answers, which we did. We had a special session in December, in the Risk Assessment Committee, where we allowed all relevant parties to provide their views on the dossier – so the industry, the NGOs from different sides, and so on. So, we had a quite extensive session to make sure that everybody was heard properly, but formally, the process which we followed is the same as the process we follow everywhere; the [standardised] way of dealing with it, which you can find on our website. So that's not unique, but the uniqueness was in that we paid a lot more attention to serving everybody's questions and to be a hundred percent transparent about the process." ECHA representative #1

The representative of ECHA emphasised that one of the reasons why the scientific evaluations of the IARC and ECHA diverge - even though they had the same focus and scope - is that the two agencies followed different procedures: while ECHA is mandated to follow Regulation ((EC) No 1272/2008 in its hazard classification tasks, the IARC follows different evaluation criteria: "The IARC and ECHA focussed on the same aspects [they both conducted hazard classification of glyphosate]. The IARC is only focussed on hazard

identification and hazard classification, and we do the same under the CLP [Regulation ((EC) No 1272/2008], because with the classification, you look at the available information on the substance, and whether it fulfils certain criteria for being carcinogenic, for instance. So, you have all these classes of hazards, which are indicated in Annex VI of the CLP. That is our task. We directly compare the information on the chemical to the criteria and then provide the view whether the substance should be classified or not. In essence, the IARC does the same, but they work on slightly different criteria; although I think they are not that different if you look at the wording. The main difference is probably what you're interested in, why we came to different conclusions." ECHA representative #1

This observation was reiterated by many (regulatory) agencies working at the Member State and EU levels. For instance, the German Federal Institute for Risk Assessment (BfR) has argued that the IARC has "no hazard classification" compatible with "CLP [EU] criteria" (BfR representative #3; BVL representatives #4; EFSA representative #2). It could be concluded, then, that ECHA (and EFSA, BfR) and the IARC use widely different classification criteria, which may alter the conclusions of the scientific evaluations.

To summarise, the desk research and semi-structured interviews suggest that one of the explanatory factors of why scientific divergences emerge between agencies (the IARC and ECHA) assessing hazards of pesticides is the different procedures and regulations followed in the scientific evaluation processes.

Internal/external control mechanisms

ECHA communicates that it is committed to providing "a service that meets the needs and expectations of its various stakeholders in a balanced and impartial way and in strict compliance with applicable legislation" (ECHA, 2018d). The Agency's integrative approach to internal quality management combine the European Commission's Internal Control Standards for effective management and the internationally recognised ISO 9001 standard for quality management systems. This approach assures good governance to obtain full stakeholder confidence and satisfaction. ECHA notes that "performing to excellent standards while meeting the requirements of our stakeholders and ensuring the consistent implementation of the REACH, CLP, Biocides and PIC Regulations" (ECHA, 2018d) is at the core of ECHA's Quality Policy.

In conclusion, the analysis of primary documents and the interview with the ECHA representative suggest that ECHA followed the standard procedures and policies in their glyphosate scientific evaluation. Even though ECHA received much criticism from various groups of stakeholders regarding its independence and transparency policies, it was responsive to this criticism by justifying or improving its practices.

The Federal Institute for Risk Assessment (BfR)

Mandate and accountability mechanisms

The BfR was established in November 2002 in order to assist consumer safety (BfR, 2018b). Their main focus lies in the assessment of associated health risks of foods, chemicals and

other products. Those assessments are then meant to assist federal ministries during decision making processes.

The BfR is in charge of consumer protection in Germany. Based on risk assessment, its purpose is to advice policy-makers in Germany and Europe and to contribute to national and international committee work. In order to contribute to the risk assessment, the BfR conducts risk assessments based on the focus points. Besides risk assessment, it plays a key role in risk communication in order for consumers to have a better understanding of associated risks of certain goods. In order to make decisions which are not influenced by political, economic or social factors, the institute is – as stated in its founding law – independent in its decisions (BfR, 2017b).

Focus of the BfR's work:

- Evaluation of health effects of biological and chemical substance security of foods
- Evaluation of health effects of chemicals, biocides, pesticides, food packaging, cosmetics, tobacco etc.
- Evaluation of health effects of GMO's
- Risk communication
- Development and validation of food supplements
- Methodology development/validation of national reference laboratories.

Source: (BfR, 2017f)

The BfR supports and secures academic expertise through its independent research, which is financed purely through public funding (BfR, 2018b). The BfR does not receive funding from third parties, which is meant to reduce social influences and maintain political and economic independence neutrality: "All the activities of BfR are only financed by public sources. There is absolutely no funding from the industry, the BfR follows the rule of independent science which are published in publicly available several documents." BfR representative #3

The BfR is part of the Federal Ministry for Nutrition and Agriculture (BMEL) and its main function is to advise the Federal Government (BfR, 2017h). It directs the risk evaluation statement towards all public institutions which are in any way related to public health and consumer security such as federal and state ministries, authorities at state, province and municipality level, consumers' associations and other unions, NGO's, research institutions, national and international organisations, and media. The media consumer associations base their information on the BfR and play a key role in informing the general public (BfR, 2017e).

The BfR is the national centre for the communication between EFSA and all German institutions (various agencies) which are related to food and animal feeds safety, such as the Federal Ministry of Food and Agriculture (Bundesministerium für Ernährung und Landwirtschaft (BMEL)), the Federal Ministry of Health (Bundesministerium für Gesundheit (BMG)) as well as the Federal Ministry for Environment, Nature

Conservation, Building and Nuclear Safety (the Bundesministerium für Umwelt, Naturschutz, Bau und Reaktorsicherheit (BMUB))(BfR, 2017c).

Independence and transparency policies

The BfR communicates that "transparency is a fundamental aspect of the work of the BfR which is essential for sound and trustworthy risk communication" (BfR, 2017a). Conflicts of interest must be recorded in writing. The members of scientific committees sign a declaration which is made publicly available by the BfR. Furthermore, "oral inquiries about topics dealt with by the committees which could conflict with the interests of the members are made at the start of every meeting and the results are recorded in the minutes" (BfR, 2017a). The minutes of the meetings that form the basis of the scientific opinions of the committees are also made available to the general public.

Selection of scientific experts

The BfR Committees: 16 committees[20] give external and independent input based on expert knowledge (BfR, 2017b). Their tasks are to advise the BfR in conceptual and methodological questions, as well as to contribute to the scientific work through independent research and evaluate those studies which are included in the risk evaluation. It increases the quantity and quality of research which is taken into consideration by the BfR. Additionally, in times of crisis, the consultation through those committees allows for quick advisory decisions. The experts of those committees have a purely advisory purpose and are not included in the final advisory decision, in order to insure an independent outcome. Please consult the table below to learn more about the appointment procedures followed at the BfR.

Appointment procedure

"Three appointment procedures have been carried out (2007, 2010, 2013) since the establishment of the BfR committees. Within the scope of a comprehensive and transparent appointment process, all of the experts interested in getting involved in a BfR committee are invited initially per public announcement to submit their applications. The appointing panel set up especially for this purpose then selects suitable candidates from the group of applicants. The appointing panel is made up of members of the BfR Scientific Advisory Board, the chairs of the German Research Foundation's (DFG) Senate Committees for the Health Assessment of Food and of Substances and Resources in Agriculture, and a representative of the Senate of Federal Research Agencies.

[20] Consumer Products; Assessment of Intoxications; Biological Hazards; Nutrition, Dietetic Products, Novel Foods and Allergies; Exposure Assessment, and Exposure Standardisation; Feeds and Animal Nutrition; Genetically Modified Food and Feed; Hygiene; Contaminants and Other Undesirable Substances in the Food Chain; Cosmetics; Food additives, Flavourings and Processing Aids; Pesticides and their Residues; Pharmacologically Active Substances and Veterinary Medical Products; Risk Research and Risk Perception; Wine and Fruit Juice Analyses; Breast Feeding (BfR, 2017)

The appointing panel nominated a total of 187 experts as BfR committee members for the period 2014 to 2017. They come from universities and other research institutions, national and regional authorities, trade and consumer associations, private laboratories and industry. Overall, roughly 50 of the experts come from universities and university clinics, including poison information centres, and non-university research institutions such as the Fraunhofer institutes, 34 % from authorities such as the federal research institutions and regional investigation offices and 16 % from enterprises and industrial associations. Around 12 % of the committee members do not work in Germany" (BfR, 2017a).

Procedures

See EFSA procedures discussed above, of which the BfR is a part of, acting as a Rapporteur Member State (RMS).

Internal/external control mechanisms

The BfR has been certified in accordance with Quality Standard DIN EN ISO 9001 since 2010 in all of its working areas: science, assessment, communication and administration. The BfR rigorously implements its Quality Management System and communicates that "Authorities, especially scientific institutions such as the BfR, must now also demonstrate that they comply with internationally recognised standards, and they must ensure such compliance by means of a functioning quality management system (QMsystem)" (BfR, 2018a).

Quality policy of the BfR

"With its quality management, the BfR pursues the following goals:

- Ensuring the best possible quality for scientific findings
- Focus on consumer protection
- Preserving scientific independence
- Ensuring economic service delivery
- Safety in the future through forward-looking planning and flexibility
- Critical assessment and monitoring of all research findings, before they are communicated to the public or a job initiator
- Use of confirmed data and verified and / or validated methods and models; the quality management of the BfR is based on the most stringent national and international standards
- Disclosure of limits and uncertainties of any research findings" (BfR, 2018a).

The analysis of primary documents and two interviews with the representatives from German regulatory authorities (BfR and BVL) suggest that the BfR strictly followed the standard procedures and policies in their glyphosate scientific evaluation (BfR representative #3; BVL representatives #4).

2. International Organisations

The International Agency for Research on Cancer (IARC)

Mandate, funding and accountability mechanisms

The International Agency for Research on Cancer (IARC) is the specialised cancer Agency of the World Health Organization (WHO). It was created in 1965 by a resolution of the World Health Assembly. It is important to note that, even though the IARC is called an 'agency', its hazard classifications do not serve regulatory purposes.

The IARC has the main objective of promoting interdisciplinary and international collaboration in cancer research. The organisation brings together experts from various fields such as epidemiology, biostatistics and laboratory sciences to identify the causes of cancer, as well as its designing preventive measures (IARC, 2018c).

As a part of the United Nations (UN), the IARC has a complex governing body. According to the 2014 Agency Statute, the main governing body of the IARC is composed of the Governing Council, the Scientific Council and the Secretariat (IARC, 2014b). As a specialised agency of the World Health Organization (WHO), the IARC is UN-sponsored, meaning it "follows the general governing rules of the UN family" (IARC, 2018d). The Director-General of the WHO sits on the IARC's Governing Council, therefore, the IARC is directly accountable to its parent organisation. The IARC is also financially accountable to the WHO, most notably through the IARC and WHO Financial Regulations and Financial Rules.

The IARC's activities are funded through two main sources. One is statutory contributions, which are provided by the participating member states (IARC, 2018a). Other funding is provided by voluntary contributions. These contributions are derived from competitive grants, but also progress through direct contributions from funding agencies ranging from charities to government organisations. These voluntary contributions are allocated to specific programmes and projects, which often happen at the request from a certain donor or organisation. The IARC also receives donations from private individuals, however, the independence polities strictly regulate which individual contributions can be accepted and which ones must be declined. These individual contributions are part of the Agency's Undesignated Contributions account. The Governing Council allocates money to certain programs and projects from the Agency's Undesignated Contributions account.

Transparency policies

The IARC has implemented various policies in order to make its research as transparent as possible. In the Agency's Medium-Term Strategy for 2016-2020, the Governing Council highlights five key values that underpin IARC's actions: honesty, integrity, independence, courtesy and generosity (IARC, 2015a). Within this, the Agency states that transparency "is required of all public institutions, but honesty goes further" (IARC, 2015a). Therefore, the IARC sees its function in not only making information freely available, but also explaining this information, including "its caveats, complexities and subtleties" (IARC, 2015a). This, it is argued, will build a "greater degree of trust" in the Agency (IARC, 2015a).

In the Medium-Term Strategy for 2016-2020, the previous policy strategies regarding transparency are also touched upon; the Agency argues that these efforts have supported "the research Sections in implementing their activities" (IARC, 2015a). The same text also draws attention to further policy decisions, such as the implementation of "new tools for systematic review, [standardising] literature searches and creating databases of information on study designs and results" (IARC, 2015a). These policy decisions will serve to "increase transparency and efficiency in the Monographs" (IARC, 2015a).

Independency policies

The IARC has a specific code of scientific conduct. In this document, the IARC outlines that their mission is "to accomplish the work outlined in the Statute to the highest standards possible, both scientific and ethical; to become the leading international centre in research for cancer prevention and provide leadership to the international community engaged in research in cancer prevention and control worldwide" (IARC, 2008, p. 8). The IARC has composed numerous principles to ensure their code of scientific conduct. These are the principles as they are outlined in the scientific code of conduct (IARC, 2008): Integrity, transparency, impartiality, independence. The IARC emphasises that their independence allows them to provide reliable and authoritative assessments of the different aspects of cancer information.

Selection of scientific experts

The IARC currently has around 300 members of staff from over 50 different countries. According to the 2014 Statute of the Agency, "the staff of the Agency shall be appointed in a manner to be determined by agreement between the Director-General of the World Health Organization and the Director of the Agency" (IARC, 2014b, p. 13). Staff members (excluding the members of the SC) - principally scientists - are usually recruited from low- to medium-income countries and "geographical representation shall also be given full consideration" (WHO, 2013). This is because the IARC is interested in developing a new generation of scientists, especially in places with scarce health services. Moreover, applicants should fulfil the following criteria: (1) Applicants cannot be related to any actively working staff members employed by the IARC; (2) Candidates must be between 20 and 62 years old (IARC, 2013). Both the IARC and the World Health Organization are transparent with selection procedures. The appointment of directors and high-ranking staff can be found on the Agency's webpage.

The IARC has strict policies in terms of who can be involved in the production of its scientific outputs (i.e., monographs). Scientific experts that have a clear conflict of interest are only allowed to participate in a limited capacity (IARC, 2014a). This is to assure public confidence. If this is the case, the scientific experts will not serve as the meeting chair or the subgroup chair, contribute to text that pertains to the description or analysis of scientific data, nor participate in any evaluations of such nature. Experts that fall under this category and pose a threat with their conflict of interest will only be invited to meetings in which they are necessary due to publishing relevant papers concerning the rates of cancer and all conflicting interests will be disclosed (IARC, 2014a).

For the IARC to assess any active substance, and in this case glyphosate and 2,4-D, the agents (not 'active substances', but ***the formulations used in the real-world situations*** *such*

as Roundup produced by Monsanto) must comply with two important criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity (IARC, 2006). A special "Ad-hoc Advisory Group" is then convened to assess the existing literature and findings to then determine the appropriateness of studying and examining such an agent. In the case of glyphosate, the Advisory Group concluded that it was pertinent to study the agent in March 2015 (IARC, 2017d). In the case of 2,4-D, the Advisory Group concluded that it was pertinent to study the agent in August 2016.

Procedures

After the Ad-hoc Advisory Group has determined the appropriateness of studying a certain agent based on the existing literature, IARC starts setting up a Monograph. A Monograph is a document in which the Agency states the findings and conclusions on the carcinogenic effects of a certain agent. In assessing glyphosate and 2,4-D, at least five categories of participants were present at Monograph meetings. These are:

The Working Group: The tasks of this group included "[selecting] and [summarising] the data relevant for the evaluation of glyphosate" as well as the data on mechanisms of carcinogenesis. Working Group Members have generally "published significant research related to the carcinogenicity" (IARC, 2006) and are selected based on "(a) knowledge and experience and (b) absence of real or apparent conflicts of interests" (IARC, 2006). In the cases of glyphosate and 2,4-D, special consideration was given to demographic diversity. In the case of glyphosate, a Working Group of 17 experts from 11 countries met at the International Agency for Research on Cancer in March 2015 to review the available published scientific evidence and evaluate the carcinogenicity of glyphosate formulations. Pertaining specifically to 2,4-D research, in 2015, 26 experts from 13 different countries met to assess the carcinogenicity of the herbicide, 2,4-D.

Invited Specialists: These are selected to contribute unique knowledge and experience to the assessment of the active substance. In the case of glyphosate, only one specialist was invited: Christopher Portier. Dr. Portier is a scientist at the US National Center for Environmental Health and the US Agency for Toxic Substances. In the case of 2,4-D, no specialists were invited to consult on the investigation, and no forms of conflicting interests were reported by the Secretariat.

Representatives of National and International Health Agencies: These representatives are invited because their governments' agencies sponsor the investigation programme. In the case of glyphosate, representatives from the Tunisian, American and French agencies were invited as these countries significantly contributed to the research on the agent. Representatives do not chair meetings, draft parts or enable actions at Monograph meetings. In the case of 2,4-D, representatives from the Brazilian, American and French agencies were invited.

Observers with Relevant Scientific Credentials: These observers are invited to stimulate the objectivity of the Monograph meeting. IARC prioritises participants with "constituencies from differing perspectives". Observers have, however, limited responsibilities and may only participate in certain discussions. In the case of the

glyphosate Monograph meetings, observers from Denmark, France, England and Germany were invited to attend.

The IARC Secretariat: These are the scientists who are designated by IARC and have relevant expertise. The IARC secretariat "serve as rapporteurs and participate in all discussions" (IARC, 2006).

In addition to these five categories, all members who participate in the Monograph must complete a "WHO Declaration of Interests" in which they report their "financial interests, employment and consulting, and individual and institutional research support" (IARC, 2016b). Moreover, "it is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time" (IARC, 2016c)[21].

The IARC tries to design a method that objectively studies the carcinogenic effect that active substances have, while simultaneously aiming to achieve a geographically representative group of assessment staff that includes different discourses into its research process.

To conclude, based on the analysis of publicly available documents and semi-structured interviews with the representatives of (regulatory) agencies (EFSA, ECHA, BfR), the IARC did not deviate from its procedures and policies when assessing glyphosate and 2,4-D hazards.

3. Regulatory agencies outside the EU

US Environmental Protection Agency (US EPA)

Mandate and accountability mechanisms

The US EPA is the American regulatory agency dedicated to protecting human health and the environment (US EPA, 2017a). The US EPA is required to develop policies, aims at fair and effective policy enforcement, using quality information, engaging stakeholders, and consulting with global partners. In achieving its goal, the US EPA develops and enforces regulations, provides grants for research and projects, sponsors private sector partnerships, and educates people about the environment.

The EPA is classified as an independent regulatory agency, meaning it is given statutory grants from Congress to act autonomously in creating regulation for specific issues (the regulations the US EPA creates can become federal law directly) (EPA, 2017a). These statutes include, for example, the Clean Air Act, which grants the EPA the power to set a national air quality standard (US EPA, 2017a). Unlike most independent agencies in the EU, the US EPA differs in that it is headed by a single administrator who is appointed by the President and approved by the Senate. The administrator of the US EPA is present at cabinet meetings but does not officially belong to the cabinet – as the powers of the agency

[21] A complete list of the participants on the glyphosate *Monograph* Meeting can be found here.

are granted by congress (in the form of congressional statutes) and not by the executive branch. In fact, the administrator of the EPA is accountable to the Congress, though the President has the ability to fire them. Another way the Congress increases the agency's accountability is be requiring transparency – which it does by passing laws such as the Freedom of Information Act (EPA, 2017a).

Other notable congressional statutes regarding the EPA's powers can be found in the Atomic Energy Act, Clean Water Act, Endangered Species Act, Energy Policy Act, Federal Insecticide, Fungicide, and Rodenticide Act, Pesticide Registration Improvement Act, and the Pollution Prevention Act (EPA, 2017a).

Independence and transparency policies

The US EPA has four guiding principles in conducting risk assessments: transparency; clarity; consistency; and reasonableness. In terms of transparency, the US EPA states the [characterisation] should fully and explicitly disclose the risk assessment methods, default assumptions, logic, rationale, extrapolations, uncertainties, and overall strength of each step in the assessment (EPA, 2014a).

The US EPA, by definition, is an independent US government agency. Thus, it is subjected to Title 2 of the Code of Federal Regulations, section 200.112, which mandates that the EPA comply with comprehensive audits designed to prevent conflicts of interest in their independent committees. Despite this commitment, the US EPA has struggled with independence issues: for example, the Flint Water Crisis was largely caused by a biased Scientific Advisory Board that favoured industry and economic efficiency over the health of individual (Volcovici, 2017). Currently, the US EPA is undergoing large-scale changes under the Trump Administration and its appointed head Scott Pruitt. Mr Pruitt, is claimed to be "politicising" the US EPA by removing scientific experts from many independent panels. Pruitt's critics — such as Tom Carper, top Democrat on the Senate Environment Committee — claim that Pruitt's decision was part of an EPA effort to "delegitimise the work of nonpartisan scientists" as part of a larger effort to transform the agency's purpose from protecting human and environmental health to promoting business interests (Volcovici, 2017).

There have been questions about the independence of the US EPA when it comes to their risk assessment of glyphosate. The US EPA was widely criticised as a result of their move to postpone the Scientific Advisory Panel advisory meeting because CropLife America (an industry trade group representing Monsanto and other pesticide companies) objected to one of the members on the panel (Center for Biological Diversity, 2017). The member that they objected to (Dr. Peter Infante, a researcher with the National Institute for Occupational Safety and Health) was subsequently removed from the panel after CropLife accused the scientist of bias (Center for Biological Diversity, 2017).

In addition to this, documents revealed in court showed that the chair of the US EPA's Cancer Assessment Review Committee on glyphosate was in regular contact with Monsanto, providing insider information that guided Monsanto's messaging (Center for Biological Diversity, 2017). Furthermore, the chair warned Monsanto that the IARC had found glyphosate to be a probable carcinogen month before the 2015 IARC Monograph on

glyphosate became public, which reportedly allowed the company to mount a public relations attack on the finding. A Monsanto executive emailed other company officials that they could hire academics to put their names on glyphosate research papers written by Monsanto, citing a previous instance where this was done (Center for Biological Diversity, 2017).

The US EPA has also received criticism by other agencies (such as the French ANSES) on the basis that the investigative mechanisms used were incomplete and inadequate (ANSES, 2016b). However, the 2017 US EPA Panel reaffirmed that the previous risk assessment of glyphosate had used a "sound, appropriate and acceptable approach" and that the US EPA "correctly addressed the issue" (US EPA, 2017). The 2017 US EPA Panel again concluded that there is "no reliable evidence of an association between glyphosate exposure [and cancer], even [considering] the possibility that some of the studies reviewed were subject to potential biases" (US EPA, 2017). That being said, the US EPA discredited arguments that claimed that certain risk-assessment procedures were subject to corporate interests that had induced bias into the research itself.

In their written responses to the questions of this study, the US EPA specified how those processes and criteria were applied to the case of glyphosate: the "EPA routinely completes independent scientific risk assessments and strives to achieve transparency in the risk assessment process and scientific outputs for all pesticide review cases. The same amount of consideration was given to glyphosate, however, EPA provided additional opportunities to solicit technical advice and feedback from independent experts and the public due to the high level of public interest. For instance, the evaluation of the human carcinogenic potential of glyphosate conducted by EPA was presented to the FIFRA SAP. As part of this process, all supporting documentation was publicly available, which included full study reports, the Agency's individual study reviews (data evaluation records, or DERs), and the Agency's issue paper detailing the process and decisions undertaken to reach the conclusions based on a weight-of-evidence approach. The transcript to the glyphosate FIFRA SAP meeting is also available." US EPA representatives #7

Selection of scientific experts

It is in the US EPA's mandate to ensure its actions are based on strong scientific data, analyses, and interpretations (US EPA, 2016). The US EPA's primary mechanism for doing so is the Science Advisory Board (SAB). The SAB is responsible for reviewing the quality and relevance of the information used to inform the EPA regulations. Additionally, the SAB reviews and influences the US EPA's research programs and plans; provides scientific advice to the EPA administrators; and advises the agency on broad scientific matters (US EPA, 2016). The SAB works in tandem with the US EPA's advisory committees: it oversees the formation of the committees (and panels) to ensure quality and balanced expertise; it advocates committee transparency; and it provides the committees with policy, technical, and administrative assistance (US EPA, 2016). Currently, the SAB is comprised of a mix of professors, public sector employees, and private sector experts, many of whom work for pharmaceutical companies (US EPA, 2017). It must be noted that the current head of the US EPA, Scott Pruitt, is pushing to exclude public sector employees/government grant recipients from the SAB (Northerly, 2017). If Pruitt's proposal is passed, private sector

scientists (many of whom are at least partially funded by industry) will replace expert scientists that were previously selected by the US EPA (Northerly, 2017).

The SAB is a Federal Advisory Committee, and thus it is subject to the Ethics in Government Act of 1978. It is therefore required by law to be fairly balanced in terms of the points of view represented and the functions to be performed by the advisory committee, and in ensuring contemporaneous public access and public input into the advisory process (US EPA, 2002). Consequently, a complex process is involved in forming SAB Panels**.** When an agency brings an issue or a project to the SAB, the board first identifies the field(s) from which experts would most appropriately be selected. Following this preliminary step, actors such as the US EPA, the public, NGOs, and industry nominate potential panellists.

The next stage in the selection process is the formation of a Short List. Criteria for evaluating prospective Short List members include: expertise, knowledge, and experience; availability and willingness to serve; scientific credibility and impartiality; and skills working in committees and advisory panels (US EPA, 2002). All candidates must fill out a Confidential Financial Disclosure Form for Special Government Employees Serving on Federal Advisory Committees at the US Environmental Protection Agency in order to gauge their conflicts of interests. If a conflict is found, the expert is often removed from the selection process. In some cases, however, when a candidate panel member possesses special knowledge or skills, the SAB Staff Director can grant a waiver that will allow an individual to serve on a panel. In this event, the US EPA issues a public notice explaining the conflict of interest and justifying its choice. The SAB staff publicises the names and bio sketches of all Short List candidates. People are invited to provide the Board with information, analysis, and/or documentation regarding candidates — all of which is considered in the final panel selection. The final panel selection is executed by the SAB Staff Director, in consultation with SAB leadership. The criteria for this final selection are: helping the Board meet EPA's legal requirements; being transparent and open to public input, so that the public can understand and participate in the process; and helping the Board fulfil its mission (US EPA, 2002).

In their written responses to the questions of this study, the US EPA specified how those processes and criteria were applied to the case of glyphosate: "The glyphosate registration and registration review team is composed of more than two dozen staff with expertise in various disciplines, including toxicology, pharmacology, epidemiology, chemistry, biology, environmental fate, entomology, statistics, risk management, and communications. Like in all executive agencies, EPA employees are subject to the employee standards of ethical conduct issued by the US Office of Government Ethics. These standards provide specific assurances to help guarantee impartiality. EPA employees maintain a high level of ethical conduct to maintain the public trust.

Furthermore, members of FIFRA Scientific Advisory Panel are classified as "special government employees" and are similarly subject to ethical screening and training as required by the office of government ethics to ensure members do not have conflict of interest and can render impartial advice. For glyphosate, panel members were selected based on their knowledge of core expertise needed for the evaluation of the human

carcinogenic potential, such as epidemiology, animal bioassays, and genotoxicity." US EPA representatives #7

Procedures
The US EPA has a standardised formula for assessing the risk of chemicals (including plant protection products). It divides risk into two categories: human health and ecological. The initial stage of risk assessment involves the collection of extensive data on the three key factors to risk: the quantity of the chemical that is/will be present in relevant environmental mediums (e.g. soil, air, water), how much exposure a person or ecological receptor makes/will make with the environmental mediums, and the inherent toxicity of the chemical (EPA, 2017b). The US EPA claims to recognise the impossibility of conducting a perfect risk assessment, and thus they pledge to openly present all of the uncertainty in their calculations and to provide a characterisation of the reliability of their estimates (EPA, 2017). While the general procedural steps described above apply to all of the US EPA approved chemicals, the process is often much more complicated, especially when there is limited understanding of a controversial substance.

In its responses, the US EPA emphasised that "EPA uses the same standard risk assessment procedure for all pesticides. Each step, in risk assessment (planning, hazard identification, dose-response assessment, exposure assessment, and risk characterisation), follows standard criteria" US EPA representatives #7

Internal/external control mechanisms
When conducting risk assessments, the US EPA must comply with statutory requirements and mandates set by Congress. These include the following (US EPA, 2002):

(A) The substance of the information should be accurate, reliable and unbiased. This involves the use of: The best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies and data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies the use of the data).
(B) The presentation of information on human health, safety, or environmental risks, consistent with the purpose of the information, should be comprehensive, informative, and understandable.

To conclude, the US EPA – in their written responses to the questions of this study – confirmed that they have followed all the formal procedures and policies in their scientific evaluations of glyphosate, 2,4-D, bentazone and neonicotinoid pesticides (US EPA representatives #7). Furthermore, the US EPA has emphasised that it is "confident in its risk assessment and its conclusion that glyphosate is not likely to be carcinogenic to humans. The EPA's conclusion is consistent with other countries and regulatory authorities including the Canadian Pest Management Regulatory Agency, Australian Pesticide and Veterinary Medicines Authority, the European Food Safety Authority, the European Chemicals Agency, German Federal Institute for Occupational Safety and Health, The Joint FAO/WHO Meeting on Pesticide Residues, the New Zealand

Environmental Protection Authority, and Food Safety Commission of Japan." US EPA representatives #7

II – Conclusion

The chapter has assessed the formal mandate and accountability mechanisms, independence and transparency policies, scientific experts' selection policies, procedures followed in the scientific assessments, internal/external control mechanisms of the five agencies: The European Food Safety Authority; the European Chemicals Agency; the German Federal Institute for Risk Assessment; the International Agency for Research on Cancer; and the United States Environmental Protection Agency. The empirical analysis of primary documents and the semi-structured interviews with agency representatives (i.e., EFSA, ECHA, BfR, BVL, ANSES, US EPA, APVMA) suggest that the agencies followed all the formal procedures and policies in their scientific evaluations of glyphosate, 2,4-D, bentazone and neonicotinoid pesticides (imidacloprid, clothianidin, thiamethoxam). However, stakeholders of the agencies (e.g., NGOs, scientific community) and institutions in charge of researching/monitoring agencies' independence and transparency policies have expressed some concerns. In response to the criticism, in recent years, the agencies – especially, EFSA and ECHA – have worked to improve their independence and transparency policies and practices.

The analysis of primary documents and the semi-structured interviews have shown that the IARC is distinct from risk assessors working in the regulatory context (e.g., BfR, EFSA, ECHA, the US EPA). First, the IARC has a different mandate and organisational mission. Second, the IARC and other agencies (working in the regulatory context) follow diverse regulations and rules in their scientific evaluation processes.

Differences in mandates and accountability mechanisms

The IARC does not directly contribute to national or international regulatory processes. The *Monographs* of the IARC provide scientific evaluations of cancer hazards based on a wide-ranging review of the relevant scientific literature, including open peer reviewed literature and industry-produced studies. Once finalised, IARC *Monographs* are considered as one of the most trustworthy and reliable scientific information on which national and international organisations may (if they choose so) rely and introduce protective measures in their national regulations, legislation, or public health intervention. However, it is important to note that it remains the discretion and responsibility of national governments to introduce corresponding regulations.

On the contrary, the risk assessments provided by agencies and bodies (e.g., EFSA, ECHA, BfR, the US EPA) working in the regulatory context carry different implications. They are designed to provide scientific advice that informs risk managers about possible risk management measures. As a result, risk assessments carried out by agencies working in the regulatory context are designed for different purposes: they have regulatory implications, i.e. based on agencies' risk assessment, risk managers take regulatory

decisions (e.g. suggestions for bans, limitations and restrictions of certain uses of pesticides).

Differences in procedures

There is substantial variation in how scientific assessment procedures are organised by the IARC and risk assessors working in the regulatory context. The analysis has revealed that the regulations and procedures followed by EFSA, ECHA and the US EPA are highly standardised and formalised (in particular, this is the case in the American regulatory system). As regards the EU, the processes are detailed in complex regulations (Regulation (EC) No 1107/2009 and relevant legal acts) and international and EU-level guidance documents (e.g. guidance document issued by EFSA on how the risks to bees should be assessed in the EU). Risk assessors working in the regulatory context have little room to manoeuvre and – as the desk research and the semi-structured interviews have shown – they strictly follow the required steps, rules and regulations in their scientific evaluation tasks.

In a similar vein, IARC *Monographs* are conducted according to the published and standardised procedures. However, the IARC, being not a regulatory body, does not have to follow the EU/US rules and regulations specifying scientific assessment procedures.

Chapter 4

I – Comparisons of scientific aspects of evaluations

This chapter reviews the scientific aspects of evaluations conducted by regulatory agencies and bodies. More specifically, it focusses on the following scientific (quality) standards: the type of evidence used in the evaluation (e.g., industry research, academic studies) and data collection methods and scientific approaches followed to evaluate the collected data (e.g., Weight of Evidence (WoE) approach).

As in the previous chapter, a sample of agencies that have conducted scientific assessments of the selected active substances are covered in this chapter. Those agencies (or bodies) include: (1) Relevant EU and EU Member State agencies (the European Food Safety Authority (EFSA), the Federal Institute for Risk Assessment (BfR), the European Chemicals Agency (ECHA)); (2) Relevant international bodies (the International Agency for Research on Cancer (IARC)); (3) Relevant agencies working outside the EU (the United States Environmental Protection Agency (US EPA)).

The core focus of the chapter is on the glyphosate case. This focus has been selected due to the public interest in the issue as well as the availability of information on this particular case, i.e. relevant agencies and bodies extensively used the case of glyphosate to illustrate various scientific aspects of their scientific evaluations. The interviewed representatives of regulatory authorities (e.g., ECHA representative #1; EFSA representative #2; BfR representative #3; BVL representatives #4; ANSES representatives #5; APVMA representatives #6; US EPA representatives #7) confirmed that the same (or comparable) scientific practices were applied in evaluating other active substances (2,4-D; neonicotinoid pesticides; bentazone).

In the remainder, the discussion on the scientific aspects of evaluations conducted by relevant agencies starts with the IARC and is followed by other agencies. This approach has been chosen to better illustrate the core differences between the IARC and other (regulatory) agencies, i.e. in the case of the glyphosate evaluation only the IARC arrived at different scientific conclusions, whereas other (regulatory) agencies concluded that glyphosate is unlikely to cause cancer in humans. For this reason, the scientific aspects of the IARC evaluation are compared to other agencies' practices.

1. International Organisations

International Agency for Research on Cancer (IARC)

Before presenting the scientific aspects of the IARC evaluation of glyphosate, one important specificity of its scientific evaluation approach has to be noted. There is one crucial difference between the IARC and other agencies' scientific assessments. Regulatory agencies worldwide (including EFSA) test only so-called '***active substance***', whereas the IARC focusses on ***the formulations used in the real-world situations***. This is the case

because the regulations and guidelines that (regulatory) agencies (e.g., EFSA) follow require agencies to respect this approach. Such an approach implies that (for glyphosate-based herbicides) only glyphosate is actually tested by regulatory agencies, not *formulations such as Roundup produced by Monsanto* (to which, for instance, farmers are actually exposed). This makes a difference in how data is assessed by agencies. For a more detailed discussion between the tests behind the *formulations* of glyphosate-based pesticides used in the real-world situations and the so-called *active substances* please see Bozzini (2017) and Corporate Europe Observatory (2018a).

The IARC was active and assertive in communicating the rigorousness of its procedures and scientific methods followed in its scientific evaluation of glyphosate (see table below).

"The IARC Monographs evaluation is based on the systematic assembly and review of all publicly available and pertinent studies, by independent experts, free from vested interests. It follows strict scientific criteria, and the classification system is [recognised] and used as a reference all around the world. This is because IARC evaluations are based on independent scientific review and rigorous criteria and procedures.
To reach these conclusions, *IARC reviewed about 1000 studies*. Some of the studies looked at people exposed through their jobs, such as farmers. Others were experimental studies on cancer and cancer related effects in experimental systems" (IARC, 2017c).

IARC's research on the effect that glyphosate (i.e., *formulations*) might have on human health was mainly based on the review of publicly available research. The evidence of the IARC Monograph Volume 112 on glyphosate was based on evidence from "reports that have been *published or accepted for publication in the openly available scientific literature*" and from "data from governmental reports that are publicly available" (IARC, 2017d). In the specific case of glyphosate, the type of evidence was mainly based on animal experimentation. For their conclusions, the IARC noted that previous investigations have shown that "glyphosate also can cause cancer in laboratory animals" (IARC, 2015). Based on the evidence, the IARC eventually concluded that there is "sufficient evidence of carcinogenicity in experimental animals" (IARC, 2015), which might also be the case in human beings.

The IARC was transparent in terms of the type and amount of data used in its scientific evaluation: "For the IARC Monograph on glyphosate, the total volume of publications and other information sources considered by the Working Group was about 1000 citations. All citations were then screened for relevance, following the principles in the Preamble to the IARC Monographs.

After this screening process, the Monograph sections on cancer epidemiology and cancer bioassays in laboratory animals cited every included study. The sections on exposure and mechanisms of carcinogenesis consider representative studies and therefore do not necessarily cite every identified study. Once published, the IARC Monograph on glyphosate cited 269 references" (IARC, 2017c).

This scientific information was identified through systematic literature searches, submissions succeeding the public call for data published on the IARC Monographs website, as well as requests to the US Environmental Protection Agency for public release of previously unpublished but relevant toxicological information. All retrieved studies were screened for relevance by experts following the principles of the IARC Monographs Preamble (see the table below).

"This screening process excluded any retrieved studies that did not provide data on glyphosate (about 80 studies) or that were not relevant to the cancer hazard evaluation (comprising about 450 studies, primarily identified through comprehensive searches for mechanistic evidence, that did not report pertinent toxicological information). Consistent with the Monographs Preamble, reviews and commentaries concerning cancer epidemiology and cancer bioassays (about 30 articles) were also excluded at this stage. Following this screening process, the Monograph sections on cancer epidemiology and cancer bioassays cited every study that provided primary data. The sections on exposure and cancer mechanisms consider representative studies to give a concise description of the relevant data and issues and thus these sections do not cite every identified study. Once published, the IARC monograph on glyphosate cited 269 references." (Deutscher Bundestag, 2015, p.2)

However, authorities that have analysed the scientific output (for instance, Deutscher Bundestag, 2015) argue that the volume of cited references may not be indicative of the comprehensiveness of an assessment: "For instance, the IARC Monograph on glyphosate cites only the study by Séralini et al. re-published in 2014, but not a further 18 related articles cited in the BfR report—comprising the now retracted original article from 2012 and commentaries thereon (15 letters to the editor, a response from the authors, and an EFSA review of the study). About 25 more reviews and government opinions cited by the BfR are not included in the IARC Monograph, which instead cites the original publications (in the sections on epidemiology and cancer bioassays, as noted above); in the sections on exposure and cancer mechanisms, preference can sometimes be given to balanced reviews in place of numerous citations. Finally, because the Monograph includes only those data relevant to cancer hazard evaluation, some 30 studies concerning non cancer adverse effects (e.g., teratogenicity, lethality) that are included in the BfR document are not cited by the Monograph." (Deutscher Bundestag, 2015, p. 3)

The method used for the IARC's risk assessment was that of a systematic review. What this entails is that the IARC would compile different results and discussions used as well as risk assessments that have already been conducted by other individual agencies (e.g., US EPA). The collection of the data was reviewed by a group of interdisciplinary working group members consisting of scientific experts which then analyse and review the studies that are already published and used in the monographs. They then evaluated the strength of the evidence and determined whether or not *the formulation of glyphosate* poses a carcinogenic hazard. Each monograph produced by the IARC collects and reviews pertinent studies and bioassays conducted on experimental animals and these are judged as to whether or not they are inadequate or irrelevant. The working group of experts decides whether or not data should be cited in regard to its relevance. To reiterate the

transparency of the agency, "*only reports that have been published or accepted for publication in the openly available scientific literature are reviewed*" (IARC, 2006).

As it becomes evident from the discussion on the type of evidence used and data collection methods, the IARC puts a strong emphasis on the public nature of the data on which their evaluations are conducted. Furthermore, they highlight the fact that their goal is to rely on independent data (which means that the IARC might exclude industry data if they consider it as not meeting their criteria): "In the interests of transparency, [the] IARC evaluations rely only on *data that are in the public domain* and available for independent scientific review. The IARC Working Group's evaluation of glyphosate included any industry studies that met these criteria. However, they did not include data from summary tables in online supplements to published articles, which did *not provide enough detail for independent assessment. This was the case with some of the industry studies of cancer in experimental animals*" (IARC, 2017c).

The data collection the IARC uses in its monographs is largely based on publicly available studies. As mentioned in Chapter 3, the Working Group of each Monograph tries to encompass a wide range of scientific investigations that also cover a wide range of conclusions. However, there has been criticism regarding how the IARC collects its data. In a Reuters article published in 2017, the news agency stated that the IARC "edited out "non-carcinogenic" findings" (Reuters, 2017) and that the agency "dismissed and edited findings from a draft of its review of the weedkiller glyphosate that were at odds with its final conclusion that the chemical probably causes cancer" (Reuters, 2017). Moreover, Reuters also noted that the IARC would not give any explanation and "won't say who made the changes or why" (Reuters, 2017). The accusations were serious and put the IARC's scientific and evidentiary procedures in a position of great doubt. As a response to the Reuters article, the IARC stated that the article is "ambiguous" and that it does not say "who is alleged to have "edited out "non-carcinogenic" findings"" (IARC, 2017b). The IARC moreover stated that the conclusions on glyphosate are the "result of scientific deliberations of Working Groups of independent scientists, free from conflicts of interest" (IARC, 2017). The IARC highlighted that its scientific procedures are very transparent in comparison to their counterpart risk-assessment agencies. The debate is likely to go on, but the IARC has claimed that its scientific, technical and evidentiary procedures (and especially data collection procedures), are transparent and free from any possible interfering bias.

In terms of scientific method used to assess the collected data, the *IARC uses the "strength of evidence" or "degree of evidence" approach*. It is important to note that IARC's *"strength of evidence"* approach has a more general meaning than the *"strength of evidence"* as defined under the procedures used by ECHA, EFSA and other regulatory agencies for evaluation of carcinogenic hazard. In other words, as emphasised by the APVMA (Australian Pesticides and Veterinary Medicines Authority), regulators (the APVMA is referring to EFSA, ECHA, US EPA, NZ EPA) do not use strength-of-evidence assessments in their scientific evaluations: they apply the 'weight of evidence' approach (APVMA representatives #6). The APVMA explains the core difference between 'weight-of-evidence assessment' and 'strength-of-evidence assessment' (see table below).

"**In a weight-of-evidence assessment**, relevant observations are validated because they are reproduced independently by different investigators/researchers. A weight of evidence assessment considers both the numbers of studies reporting a particular conclusion and the quality of the study design and data evaluation.
A strength-of-evidence assessment can be based on a single study, even if the study protocol has limitations or does not comply with internationally accepted regulatory protocols, or if the results are not consistent with observations made in other well-designed studies." (APVMA, 2017)

Furthermore, it is important to note that the IARC conducted a hazard classification (not a risk assessment). Regulatory agencies regard this as one of the key explanations why differences between the IARC and other agencies (e.g., EFSA, US EPA, APVMA) emerged.

For instance, consistent with agencies in other countries, EFSA uses a risk-based, weight-of-evidence assessment, which evaluates the full range of risks—including studies of cancer risks—and the extent to which human beings are exposed to the active substance. While a hazard-based assessment takes into account only whether an adverse effect could occur but does not consider whether it is likely to occur when used in real-life situations. To that end, agencies working in the regulatory context regard the hazard-based assessment as the first step in determining whether a pesticide poses a risk. A risk-based assessment is built upon the hazard-based assessment by defining the "likelihood and extent to which the adverse outcome will occur if the product is used according to the instructions on the approved product label" (APVMA, 2017). Please see the table below for further clarifications.

"Chemical risk assessment = hazard assessment + exposure assessment

Hazard assessment: an assessment of the data related to the intrinsic toxicity potential of an active constituent and/or formulated product

Exposure assessment [risk assessment]: an assessment of the likely exposure of humans and environmental organisms that takes into account how the chemical product is to be used, the type and formulation of the product, and the crops or animals to be treated" (APVMA, 2017)

It is important to note that the IARC hazard-based assessment of glyphosate can be best compared with the ECHA's scientific evaluation because ECHA has also conducted a hazard-based assessment, whereas other agencies (e.g., EFSA, US EPA) have engaged in the risk-based assessment. As a result, the following section starts with the discussion on the scientific aspects of ECHA evaluation before turning to the comparisons between the IARC and other risk assessors (EFSA, BfR and US EPA).

2. European agencies: EU and national regulatory bodies

European Chemicals Agency (ECHA)

ECHA bases its scientific assessment on the evaluation of studies which concern the hazards that are associated with a certain substance. In general, their assessments are triggered by the proposal of a dossier submitted for the labelling and classification of a substance (see the Classification, Labelling and Packaging (CLP) Regulation ((EC) No 1272/2008), which – in the case of glyphosate – was Germany. Once the proposal is submitted, a 45-day period of public consultation begins. This started in May 2016 and ended in June 2016 (ECHA, 2018b). The information submitted during the public consultation period can include any hazards regarding the substance. RAC can invite speakers of the general public, industry and other stakeholders to present their evidence concerning a certain substance. All submitters are requested to submit a version of their documents which includes no confidential information. The dossier submitter now has the option to react to the comments, which were provided during public consultation.

Besides the public consultation, RAC's opinion is formed through the assessment of studies chosen through a literature review by RAC. All of the included studies must follow the Good Laboratory Practice standards. In the case of glyphosate, a total of 12 studies which addressed the carcinogenic potential of glyphosate were included. Those studies were all long-term animal studies. In addition, epidemiological studies following cohort and cross-sectional designs were included. In the case of glyphosate, a total number of 347 studies were evaluated before the final opinion was formed (ECHA, 2016). The weight-of-evidence approach was followed to evaluate the compiled data.

The assessment of the associated hazard of glyphosate can be found in the harmonised classification and labelling (CLH) report (see ECHA, 2016). It provides a summary of all included studies and the classification and labelling of glyphosate. The studies are divided into human health hazard assessment and environmental hazard assessment. These two sub-classifications of the assessment are further broken down into 10 sub-categories (toxicokinetics, acute toxicity, specific target organ toxicity-single exposure, irritation, corrosivity, sensation, specific organ toxicity-repeated exposure, germ cell mutation, carcinogenicity, toxicity for reproduction) for the human health hazards and four sub-categories (degradation, environmental disruption, aquatic bioaccumulation, aquatic toxicity) that focus on environmental hazards. Furthermore, third parties can be invited by RAC to present their opinion.

In the case of glyphosate, a large number of studies was taken into consideration regarding carcinogenic properties of the substance, as this was the key concern and media focus. 12 long-term animal studies were assessed, which is ten more than in a usual evaluation. 11 of those studies took place under good laboratory practice (GLP) and further EU standards. According to ECHA, this ensures high confidence and reliability of the results, and therefore ultimately a better evaluation. In addition, a range of epidemiological studies were evaluated, including case control and cohort studies. The final evaluation by RAC is founded on the evaluation of glyphosate, which in turn is based on: (1) substance

classification for physico-chemical properties; (2) human health hazard assessment; and (3) environmental hazard assessment (BAuA, 2015). For glyphosate, over 300 documents were taken into account.

Furthermore, ECHA allowed stakeholders to give presentations to RAC in order to present their findings and opinions, which were then taken into consideration (ECHA, 2018b). One key criterion for a stakeholder to be included is the provision of the registration number in the European Union Transparency Register to ECHA (ECHA, 2018a). In December 2016, presentations by the German Federal Institute on Occupational Safety and Health (BAuA), EFSA, IARC, FAO and WHO, Glyphosate Task Force, and representatives of the Health and Environment Alliance (HEAL) took place in Helsinki (ECHA, 2016). The inclusion of third parties insures a broad range of assessed data and thus forms a control mechanism. All data coming from third parties – and taken into account when forming the final decision – are later published on the ECHA website, and all third parties are requested to provide a censored version for such publication purposes. The interviewed ECHA representative notes that this is one of the differences of how the IARC and ECHA (together with other EU agencies) work: "The IARC works really behind closed doors with regards to their monographs. Nobody can actually follow the process which is taking place there. It has been their decision to only have discussions with scientists, without any presence and therefore without any potential influence of stakeholders. And I think from our side, we claim that *our scientists are perfectly able to discuss in front of NGOs and industry*. In the end, we take a decision based on the scientific facts, but we do not mind doing so in front of the stakeholders." ECHA representative #1

In March 2017, RAC ended their evaluation that concluded that "the available scientific evidence did not meet the criteria to classify glyphosate as a carcinogen, as a mutagen or as toxic for reproduction" (ECHA, 2017b). This conclusion was in contradiction to the IARC scientific evaluation. The interviewed ECHA representative suggested that one of the reasons why scientific divergences between the two agencies have occurred is related to the differences in data sources on which they relied. The interviewee noted that ECHA had access to a wide set of data and research:

"The main difference [between the IARC and ECHA] is that in addition to information that is completely publicly available, we also take information into account which has been presented by industry. *That is part of the normal procedure*. Therefore, *we have access to a greater number of studies than the IARC has been using, and we have access to all the details behind those studies*. There is a huge amount of studies available on carcinogenicity, and the committee (RAC) has access to all underlying information, all the statistics behind it, all the details. And that is *not exactly the same as what has been happening within the IARC*. That is probably one of the reasons why the final conclusion – which, again, is a so-called weight-of-evidence conclusion – and the consensus by the members of the committee was that although some evidence in the studies indicated certain effects by the substance, the substance does not fulfil the criteria for classification." ECHA representative #1

Furthermore, the representative of ECHA clarified one important aspect that is usually misunderstood in the public debates. Namely, the IARC also draws on the industry data (not only academic studies), however, not all industry data is available to the IARC: "it's

not that we have one dataset and the IARC has another. There was a lot of overlap between the information used by both agencies. However, not all details on some studies were available to the IARC. Therefore, they could not take those studies into account, because their criterion is that studies need to be fully publicly available. And that has not been the case for all studies; *but it's incorrect to say that we only look at industry data and they only look at publicly available data. We also look at all publicly available data; in that sense, we probably have a wider database than the IARC has*." ECHA representative #1

To summarise, the core reasons for the scientific divergences between the IARC and ECHA hazard-based assessments – as illustrated by the publicly available document analysis and semi-structured interviews – is that (1) ECHA as an agency working in a regulatory context had access to data sets provided by the industry, whereas the IARC assessed only publicly available data (including industry provided data that is available in the public domain), and (2) the two agencies followed different scientific criteria in their scientific evaluation: the IARC followed the strength of evidence approach, whereas ECHA relied on the weight of evidence approach.

European Food Safety Authority (EFSA) and the German Federal Institute for Risk Assessment (BfR)

The scientific aspects of the evaluation provided by the BfR and EFSA are discussed together because - as explained in Chapter 3 on 'European agencies: EU and national regulatory bodies' - the BfR was a Rapporteur Member State in the case of glyphosate. The BfR provided EFSA with a Renewal Assessment Report (RAR) upon which EFSA based its peer review concerning the renewal of the approval of the pesticide active substance glyphosate.

The BfR based its scientific output on the evaluation of evidence on the hazardousness of glyphosate. The BfR then produced a scientific evaluation regarding the attributed risks. The BfR assessed all studies cited by the applicant in the submitted dossier. In 2015, the BfR issued a Renewal Assessment Report (RAR) which entailed the re-assessment of the opinion on glyphosate (BfR, 2017d). This opinion was then forwarded to EFSA. The re-assessment of glyphosate was attached as an addendum to the RAR.

Independently from the studies included in the industry submitted dossier, research was carried out by BfR which concentrated on the effects of glyphosate on livestock – particularly cows (Riede et al., 2016). Further studies contributing to the assessment of glyphosate were carried out by the Friedrich-Löffler-Institut and the TiHo Hannover (Von Soosten et al., 2016). The BfR emphasised in the RAR that all studies that are to be assessed (using WoE approach) and included in the formation of an official opinion have to follow the guidelines of good laboratory practice (GLP). This is to ensure high standards and quality outcomes of research worldwide.

A review of all relevant studies for the assessment of glyphosate was also carried out. According to the BfR, especially in cases raising issues of carcinogenicity, genotoxicity and endocrine disruptive substances, the literature review and the inclusion of a broad

spectrum of studies were particularly important in order to ensure an accurate assessment (BfR, 2017d). Another part of the assessment was the evaluation of the opinion of Member States through a peer review assessment of their studies and public consultation. Only after the comments of Member States were included in the report was the opinion forwarded to EFSA.

Following the requirements of Regulation (EC) No 1107/2009, EFSA provided its assessment of the active substance primarily based on Germany's (BfR) initial evaluation of hazards and risks. The EFSA-led review considered "a large body of evidence, including the IARC report"; as well as "the original studies submitted by the applicants in line with the legal requirements", "all available and published studies were considered" (EFSA, 2015e). The EFSA-coordinated German evaluation examined more than 150 new toxicology studies (compared to its earlier assessments) and re-assessed almost 300 existing toxicological studies. EFSA also considered around 900 scientific publications and reviewed more than 200 of them in detail.

Although the EU assessment did not include a number of epidemiological studies that were included in the IARC's monograph, these studies were later added to the EU dossier, meaning that, in total, "EFSA assessed more evidence including additional key studies that were not considered by IARC" (EFSA, 2015e, p.1). Thus, to summarise, EFSA's assessment was based on original studies: "mandatory regulatory Good Laboratory Practice (GLP) studies, other relevant studies and the outcome of the search of peer-reviewed scientific studies published within the last 10 years before the submission of the dossier" (EFSA, 2015e, p.1). Also, the peer-review included "a public consultation… and several commenting phases by EFSA scientists and MSs experts, the possibility for requiring additional information from the applicants, and a set of experts' meetings covering different scientific areas" (EFSA, 2015e p.1).

Furthermore, the interviewed representative of EFSA emphasised that the claims that EFSA draws on industry research, whereas the IARC relies on academic studies is not true, i.e. the IARC also based their hazard-based assessment on industry produced data. The interviewee emphasised that EFSA draws on multiple sources of evidence including both publicly available and submitted by the industry:

"First, in our assessment we both have industry-sponsored studies, as well as the review of the scientific literature. That is mandatory because of the regulation. In the case of glyphosate, we have huge amounts of scientific literature that was first reviewed by industry, because the regulation requires them to do so. Afterwards, it was re-assessed by Germany and then by EFSA and all the other Member States during the process. More importantly, there are no valid studies on glyphosate's carcinogenicity, other than the ones that have been sponsored by industry. So, when people say that the IARC's assessment is based on the scientific literature, IARC's assessment on the carcinogenic effects on animals – which is the key issue – *is based on studies sponsored by industry*. The difference is that we received the full studies, just as all other regulatory agencies, and the IARC did not receive the full studies, but only the summaries of those studies which had previously been used in regulatory assessments, including EFSA's in some cases.

In the case of glyphosate, the IARC used studies used by the US EPA, and a secondary group of the WHO called the JMPR, the Joint Meeting on Pesticide Residues. What is important is that, *based on the same studies, the US EPA and the JMPR have concluded that glyphosate was not carcinogenic in animals.* Both groups, after the IARC assessment, have revised their assessments, and have again concluded that glyphosate is not carcinogenic in animals. So, *there is a lot of misinformation: the IARC used public information, but also used public summaries of industry-sponsored studies*. There is no other available information: There were only two other studies on glyphosate's carcinogenicity that were published, and both the IARC and EFSA concluded that these studies were not sufficiently valid. Therefore, all available information on glyphosate's carcinogenicity comes from studies sponsored by industry" *EFSA representative* #2

In the scientific evaluation conducted by EFSA, over 100 studies plus additional studies encountered during the commenting period and the public consultation regarding genotoxicity were included in the revised RAR (Renewal Assessment Report) (EFSA, 2015e). EFSA considered a weight of evidence approach, "taking into account the quality and reliability of all available data", hence concluding that "glyphosate is unlikely to be genotoxic *in vivo*" (EFSA, 2015e). Furthermore, it is important to reiterate that "unpublished [mainly industry] studies that were the core basis of the peer review evaluation [of EFSA] were not available to the IARC experts as reported in the IARC monograph 112 on glyphosate" (EFSA, 2015e, p. 3). For example, out of the nine long-term rat studies EFSA examined, three of these "were not evaluated by the IARC experts" (EFSA, 2015d, p. 3).

The method of data collection employed by EFSA was to gather all available evidence, evaluate it accordingly and then use a weight of evidence (WoE) approach to draw conclusions. EFSA defines 'weight of evidence assessment' as "a process in which evidence is integrated to determine the relative support for possible answers to a question" (EFSA, 2017g, p. 1) The WoE approach comprises of three basic steps: "(1) assembling the evidence into lines of evidence of similar type, (2) weighing the evidence, (3) integrating the evidence" (EFSA, 2017g, p. 1).

Regardless of the vast evidence and rigorous scientific methods used to assess the data, EFSA and the BfR were challenged by a group of scientists. The scientific conclusions of the BfR and EFSA were heavily scrutinised. An open letter by 96 independent scientists working in academia and governmental agencies was published and arguing that the BfR "differed from standard scientific practices in order to reach their conclusions" (Portier et al., 2015, p. 5). For example, the BfR used confidential data in its research, meaning that it is impossible for an objective third-party to review the conclusions with scientific confidence (Portier et al., 2015). In addition to this, the scientists claimed that the BfR conclusions lacked citations for references, a list of authors or contributors, and an acknowledgement of conflicts of interests. In response to the accusations, on the 20th of September 2017, the BfR publicly rejected accusations of plagiarism, after a number of accusations through media organisations within Germany (BfR, 2017g). According to the BfR, it is usual that risk assessment agencies include original submitted information in their final report if those are of high significance for the final opinion. The accusations concentrated on the literary rights of the published information and summaries, as well as

literature reviews which were published to inform the public and communicate the risks associated with glyphosate.

In addition, in response to many public allegations and controversy, EFSA and BfR scholars[22] have published an open access article explaining why scientific differences between the IARC and other agencies including EFSA, BfR, ECHA have emerged. In a nutshell, Tarazona el al. (2017) argue that the scientific divergences between the IARC and EFSA have emerged because they have engaged in different types of scientific evaluations (hazard classification *versus* risk assessment), which is an important factor explaining discrepancies in scientific conclusions. Furthermore, the following factors were also identified as important causes explaining scientific divergences in the two scientific evaluations: (1) agencies relied on different data sources to assess risks; (2) they applied different scientific approaches (i.e., methodologies) to assess the collected data; and (3) they engage in different interpretations when weighing indefinite results. See the summary of the core differences in
Table 4.

Table 4 Comparison of IARC and EU regulatory assessments roles, data sources and methodological elements

Issue	IARC	EU evaluators working in regulatory environment
Role	Hazard based identification No regulatory power	Scientific assessment covering hazard identification (classification), hazard characterisation (setting toxicological reference values), exposure assessment, and risk characterisation. Formal support for decision making
Data sources	Review of published information. Summaries of industry sponsored studies used as secondary source if obtained from regulatory agency reports	Full set of mandatory (OECD guidelines) GLP studies and epidemiological data Review of scientific peer-review publications, last 10 years Information collected through a public consultation
Methods	IARC developed methodology, described in the "preamble".	For chemical pesticides, hazard identification based on UN GHS criteria Detailed guidance from ECHA available

Source: adapted from Tarazona el al. (2017)

[22] Jose V. Tarazona, Daniele Court-Marques, Manuela Tiramani, Hermine Reich, Rudolf Pfeil, Frederique Istace, and Federica Crivellente

Different types of scientific evaluations (hazard classification versus risk assessment)

The differences between the IARC and other regulatory bodies occur due to the differences between hazard and risk assessments. The hazard assessment provided by the IARC indicates "the strength of the evidence that a substance or agent causes cancer" (IARC, 2015, p.3). The Monographs of the IARC identify *cancer hazards*, i.e. the potential for the exposure to cause cancer. However, it is important to note that, according to the interviewed representatives of agencies, hazard identifications *do not imply the level of risk related with actual exposure (ECHA representative #1; EFSA representative #2; BfR representative #3; BVL representatives #4; ANSES representatives #5; APVMA representatives #6; US EPA representatives #7)*. For instance, the cancer risk associated with specific active substances assigned the same carcinogenicity classification may be very different. The difference depends on factors such as the type and extent of exposure and the strength of the effect of the substance: "While the hazard potential is intrinsic and, therefore, expected to be equivalent in all evaluations, the risk is related to the use of the substance—which is defined as the likelihood and magnitude of adverse effects—and strongly depends on the patterns and conditions of use" (Tarazona et al., 2017).

The IARC Monographs assess cancer hazards, but do not evaluate the risks related with exposure. A specific active substance is regarded as a cancer hazard if it is able to cause cancer under some circumstances. On the contrary, risk assessments measure the likelihood that cancer will occur, given the level of exposure to the active substance. As a result, according to regulatory bodies (such as EFSA, US EPA) the distinction between hazard and risk assessments is crucial. For instance, the IARC Monographs may identify cancer hazards even when risks to consumers are very low at the exposure levels they face. As a result, EFSA together with other regulatory scientists (US EPA, Canadian, Australian authorities) argue that "IARC assessments do not include recommendations regarding regulatory or legislative decisions; they are scientific evaluations informing regulatory assessments"(Tarazona et al., 2017).

However, it is important to note that the IARC disagrees with this reasoning, which is provided by the risk assessors working in the regulatory context (EFSA, US EPA). The IARC states that "the Monographs Programme identifies cancer hazards even when risks are very low at current exposure levels" (IARC, 2016a). In other words, the IARC argues that the differences in scientific conclusions occur not due to the differences between hazard classification and risk assessment practices, but other factors (e.g., data sources, scientific criteria followed in the evaluations).

Different data sources: publicly available independent studies versus regulatory science

Tarazona el al. (2017) argue that the core differences between the scientific conclusions of the IARC and other regulatory (EFSA, ECHA, US EPA) agencies and bodies have occurred because the risk assessors have drawn their scientific conclusions on different sources of data. In its scientific evaluations, the IARC relies not on 'regulatory science', but on publicly available data. The IARC "systematically assembles and evaluates all relevant

evidence available in the public domain for independent scientific review" (IARC, 2018); this included among others open peer reviewed literature and publicly available industry-produced studies. On the contrary, agencies operating in the regulatory context (such as EFSA, ECHA, US EPA) often rely on so-called 'regulatory science' that includes industry provided data as well as open scientific peer-reviewed literature. The reliance on industry data is a common approach followed by national, international and EU regulatory agencies and bodies. This is the case because companies producing pesticides are legally obliged to provide data to regulatory agencies on the toxicity (including carcinogenicity) of their products. Industry data production have to follow the strict Good Laboratory Practices (GLP). Such a system is deemed to ensure the reliability and validity of the data provided by industry. It is important to note that data delivered by industry is regarded a crucial element of the 'regulatory science' on which scientific assessments of active substances are based. The industry data are not available in the public domain due to confidentiality rules.

The interviewed representative of EFSA reiterated that one of the key reasons for differences between the IARC and other regulatory agencies was data availability: "Clearly, we have a much higher amount of information than the amount used by the IARC. Even more importantly, our experts have access to the full study reports, and IARC's experts did not have access. They only have access to summaries of the key studies, so that's a different kind of information." *EFSA representative* #2

Scientific criteria followed in the scientific evaluation

According to Tarazona el al. (2017), methodological differences in the scientific evaluations of the available evidence have been identified. The IARC developed its own methodology as introduced and explained in its "preamble" (Please see Figure 1 more detailed explanations and illustrations). On the contrary, risk assessors working in the regulatory context are constrained by the internationally or EU-level defined methodologies and guidelines that they have to follow in assessing risk. In the EU context, those include hazard identification methods based on the UN GHS criteria, as well as detailed guidance from ECHA, as clarified by the EFSA representative in the interview: "What we are using as methodology to assess carcinogenicity is what was discussed in the United Nations; there is what is called the Globally Harmonized Classification and Labelling of Chemicals. This has been implemented in the EU through the CLP regulation, the regulation on classification and labelling. EFSA is using that assessment, in line with guidelines produced by ECHA. So, for the carcinogenicity, we use criteria that are in line with those provided in the Globally Harmonized Classification and Labelling of Chemicals; and we use the ECHA guidelines. The IARC is using a different methodological approach, and maybe that may explain some of the difference." *EFSA representative* #2

Different interpretations when weighing indefinite results

The IARC and risk assessors working in the regulatory context have interpreted studies in different ways. For instance, the same weak evidence in humans for the carcinogenicity of glyphosate was interpreted in different ways by the IARC and EFSA: "The IARC considered the association between exposure to glyphosate and non-Hodgkin lymphoma as "limited evidence in humans", while in the EU assessment, most experts considered the

evidence as "very limited" and insufficient for triggering the classification" (Tarazona et al. 2017, p. 2738). The variance in the interpretation between the IARC and the EU is mainly caused by the fact that the IARC considered that "glyphosate is carcinogenic in animals, and concluded that strong evidence for two mechanisms, genotoxicity and oxidative stress, supported the plausibility of the weak association in humans" (Tarazona et al. 2017, p. 2738, see also Williams et al. 2016; Portier et al. 2016 for an alternative explanation for scientific divergences).

However, the representatives of the scientific community, in turn, criticised EFSA and BfR regarding their interpretation of the selected studies that, according to Portier et al. (2015), have led to the omission of studies when assessing the risks of glyphosate (see table below).

Open letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR

In their RAR, BfR concluded (Vol. 1, p. 160) "classification and labelling for carcinogenesis is not warranted" and "glyphosate is devoid of genotoxic potential".

- BfR agreed with the IARC on limited evidence in humans but then dismissed the association as "insufficiently consistent" with no justification.
- Using an inappropriate historical control dataset in an incorrect manner and ignoring established OECD guidelines cited in their report, BfR dismissed evidence of renal tumors in 3 mouse studies, hemangiosarcoma in 2 mouse studies and malignant lymphoma in 2 mouse studies. Thus, BfR incorrectly discarded all of the glyphosate-induced carcinogenic findings in animals as chance occurrences.
- The BfR ignored important laboratory and human evidence of genotoxicity.
- The BfR confirmed that glyphosate induces oxidative stress and dismissed this finding for lack of any other finding because they had dismissed all of the other evidence (Portier et al. 2015, p. 7).

To conclude, this study has found that scientific divergences between the IARC and EFSA have emerged because of the following reasons: (1) the IARC and EFSA engaged in different types of scientific evaluations (hazard classification *versus* risk assessment); (2) agencies relied on different data sources to assess risks; (3) they applied different scientific approaches (i.e., methodologies) to assess the collected data; (4) they engage in different interpretations when weighing indefinite results.

3. Regulatory agencies outside the EU

United States Environmental Protection Agency (US EPA)

The US EPA has obtained its data through several ways: an open literature search; studies that are submitted to the agency; and the evaluation of relevant studies. Data was collected by searching the open literature and other publicly available sources (e.g., recent internal reviews, evaluations by other organisations) (EPA, 2016). Furthermore, internal databases were also searched for industry submitted studies conducted according to the Organization for Economic Cooperation and Development (OECD) test guidelines,

OCSPP23 – harmonised test guidelines, and other pesticide test guidelines (Office of Pesticide Programs (OPP) guidelines) (US EPA, 2016). Furthermore, the agency has been encouraged by the National Academy of Sciences National Research Council (NRC) to move towards systematic review processes to enhance the transparency of scientific literature reviews that support chemical-specific risk assessments to inform regulatory decision-making (US EPA, 2016). In the written response to the questions of this study, the US EPA emphasised: "The Agency strives to use high-quality studies when evaluating pesticide chemicals and considers a broad set of data during this process. This includes registrant generated studies, typically using OECD test guidelines, required under FIFRA, as well as peer-reviewed scientific journals and other sources, such as other governments and academia. All studies are thoroughly reviewed to ensure appropriate conduct and methodologies are [utilised] and that sufficient data and details are provided. This ensures that decisions are informed by the best science available" US EPA representatives #7

As part of the evaluation of the human carcinogenic potential of glyphosate, the literature review described here uses concepts consistent with fit-for-purpose systematic reviews, such as detailed tracking of search terms and which literature have been included or excluded (EPA, 2016). To obtain literature, OPP worked with US EPA librarians to conduct searches in PubMed, Web of Science, and Science Direct (EPA, 2016).

For all pesticides, there are toxicology data requirements that must be submitted by industry to the agency for registration; these studies, defined under the 40 CFR Part 158 Toxicology Data Requirements, provide information on a wide range of adverse health outcomes, routes of exposure, exposure durations, species, and life stages (US EPA, 2016). They typically follow OECD, OCSPP, or OPP accepted protocols and guidelines, which ease comparisons across studies and chemicals (US EPA, 2016). The toxicological databases for glyphosate were reviewed and all relevant animal, genotoxicity, and metabolism studies were collected for consideration (US EPA, 2016). Studies submitted to the agency are evaluated based on OECD, OCSPP, or OPP test guideline requirements to determine whether studies are acceptable for use in risk assessment (US EPA, 2016).

To ensure the quality of the risk assessments that the US EPA conducts, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) is augmented by other experts that come from the following organisations, namely the Food Quality Protection Act Science Review Board. They also assist in reviews, as well as discussing and peer reviewing the work of the agency (US EPA, 2016).

The US EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) is currently developing systematic review policies and procedures that are part of the scientific guidelines (EPA, 2018). This means that OCSPP employs "fit for purpose" systematic reviews that rely on standard methods for collecting, evaluating, and integrating the scientific data supporting the agency's decisions (US EPA, 2016). They chose this particular concept because it implies that a particular activity or method is suitable for its intended use (US EPA, 2016). As a result, in this definition there is no 'one size fits all' and thus

[23] EPA's Office of Chemical Safety and Pollution Prevention (OCSPP)

flexibility is allowed (US EPA, 2016). However, it is important that, according to the US EPA, with this flexibility, there is transparency of documented processes, including the importance of transparency and clarity in approaches to data collection, evaluation, and integration (US EPA, 2016, US EPA representatives #7).

The US EPA uses a weight-of-evidence (WoE) approach when integrating data from multiple sources to take quality, consistency, relevancy, coherence biological plausibility, and uncertainty into account. Application of WoE analysis is an integrative and interpretive process routinely used by EPA and outlined in its risk assessment guidelines.

The representatives of the US EPA noted, in their written responses to the question of this study, "EPA's risk assessment for glyphosate was conducted independently of any other [organisation] and the IARC decision did not influence EPA's conclusions. EPA's cancer classification for glyphosate is based on a weight-of-evidence evaluation in accordance with the Agency's 2005 Guideline for Carcinogen Risk Assessment. The dataset considered by EPA included studies submitted for registration of glyphosate, as well as studies identified in the open literature as part of a systematic review. EPA also incorporated data that were not previously available into its evaluation." US EPA representatives #7

Furthermore, as other (regulatory) agencies assessed and interviewed in this study, the US EPA emphasised the core differences between their and IARC's scientific assessment, i.e. the IARC and the US EPA have relied on different data sets because not all information was available to the IARC. "The IARC only considers data that have been published or accepted for publication in the openly available scientific literature. As a result, IARC only considered a subset of the studies included in [the] EPA's evaluation. [The] EPA also did not use some studies that IARC incorporated into their evaluation because [the] EPA did not believe the studies were appropriate for determining the human carcinogenic potential of glyphosate. For example, genotoxicity studies conducted in non-mammalian species (i.e., worms, fish, reptiles, plants) were excluded from the EPA's evaluation because they were not considered relevant for informing the genotoxic risk in humans." US EPA representatives #7

To conclude, the primary document analysis and interview data suggest that scientific divergences between the IARC and the US EPA have emerged because of the following reasons: agencies relied on different data sources to assess risks; they applied different scientific approaches (i.e., methodologies) to assess the collected data; and they engage in different interpretations when weighing indefinite results.

II – Conclusion

The chapter has assessed the scientific aspects of evaluations produced by the International Agency for Research on Cancer; the European Food Safety Authority (together with the German Federal Institute for Risk Assessment); the European Chemicals Agency; and the United States Environmental Protection Agency. It has shown that several factors have contributed to the explanation relating to the main research question of this research paper: Why do risk assessors arrive at different conclusions?

The empirical analysis of primary documents and the semi-structured interviews have indicated that the scientific divergences between the IARC and other agencies (e.g., EFSA, ECHA, the US EPA) have emerged because they have engaged in different types of scientific evaluations (hazard classification *versus* risk assessment). Furthermore, the following factors were also identified as important causes explaining scientific divergences in the evaluations: agencies relied on different data sources to assess risks and hazards; they applied different scientific approaches (i.e., methodologies) to assess the collected data; and they engaged in the different interpretations when weighing indefinite results.

First, the differences between the IARC and other agencies (e.g., EFSA, ECHA, US EPA) occur due to the differences between hazard-based assessments and risk-based assessments. The *Monographs* of the IARC identify *cancer hazards*, i.e. the potential for the exposure to cause cancer. The scientific assessments of agencies are based on the risk evaluation, i.e. the likelihood and magnitude of adverse effects (which depend on the patterns and conditions of substance use). In other words, risk assessments measure the likelihood that cancer will occur, given the level of exposure to the active substance. As a result, according to regulatory bodies (such as EFSA and the US EPA) the distinction between hazard-based assessments and risk-based assessments is crucial. For instance, the IARC Monographs may identify cancer hazards, even when risks to consumers are very low at the exposure levels they face. EFSA, together with other regulatory scientists (American, Canadian and Australian authorities), argue that the IARC assessments do not include recommendations regarding regulatory decisions: rather, they are scientific evaluations informing regulatory assessments.

Second, one of the core differences between the scientific conclusions of the IARC and other agencies (e.g., EFSA, ECHA, the US EPA) have occurred because the risk assessors have drawn their scientific conclusions based on different sources of data. In its scientific evaluations, the IARC relies on publicly available data. The IARC systematically evaluates evidence that is available in the public domain (which includes - among others - open peer reviewed literature and publicly available industry-produced studies). On the contrary, agencies operating in the regulatory context (such as EFSA, ECHA, the US EPA) often rely on so-called 'regulatory science', which includes industry-provided data (not always available publicly), as well as open scientific peer reviewed literature. In other words, agencies such as EFSA, ECHA and the US EPA rely on publicly available data as well as confidential data provided by applicants (industry).

Third, methodological differences in the scientific evaluations of the available evidence have been identified between the IARC and other agencies (EFSA, ECHA, the US EPA). The IARC relied on a different methodology – defined and explained in its "preamble" – than other agencies. Risk assessors working in the regulatory context (EFSA, ECHA, the US EPA) are constrained by the internationally or EU defined methodologies and guidelines.

Fourth, there are some differences in how the IARC and other agencies (EFSA, ECHA, the US EPA) interpret studies when weighing indefinite results. That is, the IARC and risk assessors working in the regulatory context have interpreted studies in different ways. For instance, the same weak evidence in humans for the carcinogenicity of glyphosate was

inferred in different ways by the IARC and (regulatory) agencies. To illustrate, the IARC considered the association between exposure to glyphosate and non-Hodgkin lymphoma as "limited evidence in humans", whereas, for instance, in the EU assessment, most experts considered the evidence as "very limited" and insufficient for triggering the classification.

Chapter 5

I – Stakeholder Survey: Study on the European Food Safety Authority and its risk assessment practices

In addition to the desk research and semi-structured interviews, an online stakeholders' survey (entitled 'Study on the European Food Safety Authority and its risk assessment practices') was carried out from the 4th of January to the 23rd of February 2018 to collect opinions about the scientific risk assessment model established in the EU by Regulation (EC) 1107/2009 concerning the placing of plant protection products on the market. The questions explore scientific/technical, procedural, performative and ethical aspects of European Food Safety Authority's (EFSA) work on risk assessment in the field of pesticides used in plant protection products.

The survey was sent to a wide range of stakeholders and organisations (research community, national regulatory authorities, NGOs, industry, etc.). It was disseminated to 293 stakeholders, including national competent authorities, PPP manufacturers and industry organisations, health/environment NGOs and consumer groups, and research community (e.g., academics), associations of PPP users, farmers' associations. The list of potential respondents was collected on EFSA's website, i.e. EFSA publishes a list of organisations and individuals who attend its events (stakeholder consultations, conferences, other activities organised by EFSA). The survey received 42 fully completed responses (response rate: 15%) plus 25 responses that were not fully completed (response rate: 23%).

The questions of the survey were developed by Dr Dovilė Rimkutė and Dr Madalina Busuioc, Leiden University, Institute of Public Administration. The questions are theoretically motivated and draw on the organisational reputation literature (see Carpenter, 2010).

1. Distribution of the survey respondents

The largest group of respondents who filled in the questionnaire is national competent authorities (55% of all received responses), followed by industry/industry associations (15%) and NGOs and advocacy groups (12%), research community (8%) (see Figure 7). Regarding the highest education level achieved of the respondents, around 49% of the respondents have a doctoral degree, 27% master's degree and 2% bachelor's degree, while the remaining respondent have high school diploma, vocational or other qualifications. In terms of gender representation, 56% males and 44% females submitted their answers to the online survey. Representatives from the following countries took part in the survey: Italy, Denmark, Spain, Austria, Malta, Greece, Belgium, The Netherlands, Germany, Sweden, Finland, Lithuania, France, the UK, Canada, Slovenia, Norway, Croatia, Ireland.

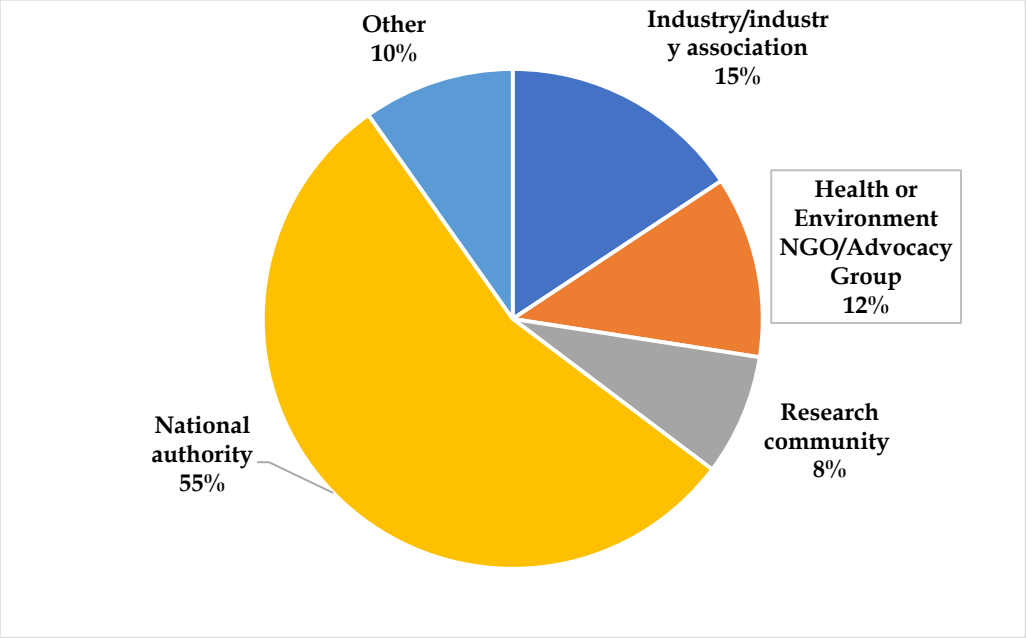

Figure 7. Distribution of the survey respondents

Figure 8 illustrates that the stakeholders that have filled in the questionnaire interact with EFSA mostly on a weekly (29%) or monthly (27%) basis.

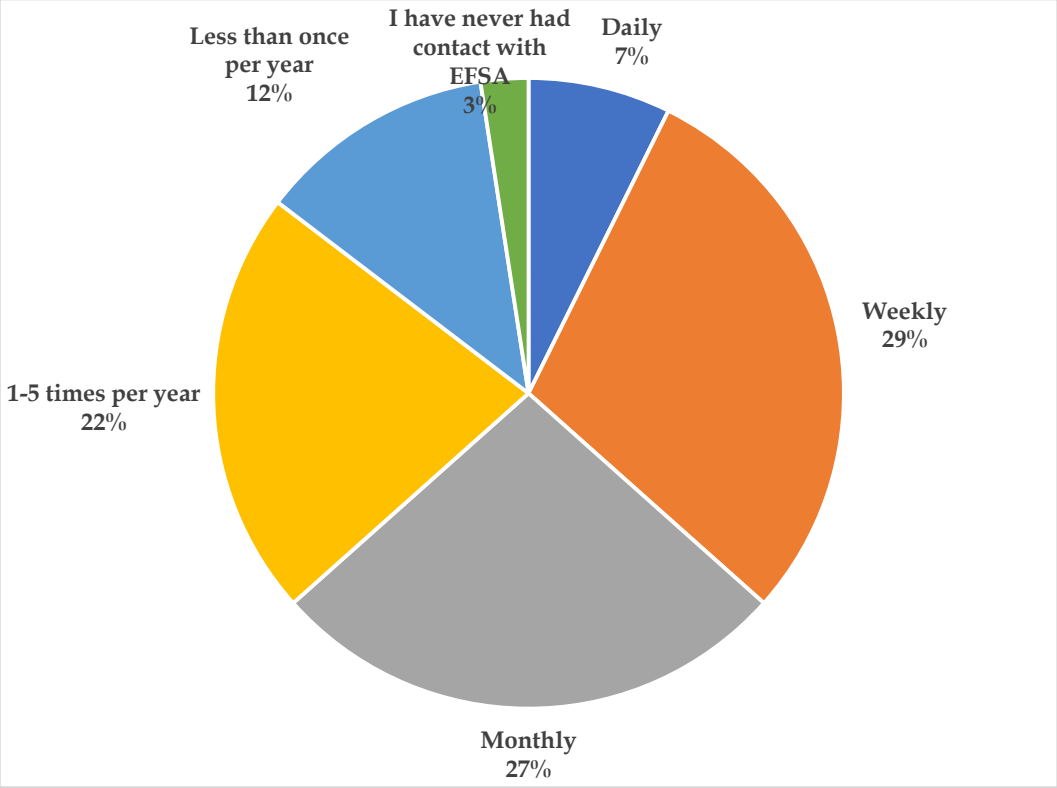

Figure 8. Stakeholders' interaction with EFSA

2. Survey results

The questionnaire consisted of 18 statements in which the respondents were asked to indicate the extent to which they agree or disagree (7-point Likert scale), with the statements regarding EFSA and its scientific work. The survey questions aimed to cover five different aspects of the day-to-day activities of the European Food Safety Authority. For this purpose, the questionnaire included from three to five statements asking respondents to express their opinions regarding the activities of EFSA in the following categories:

- Technical/scientific conduct of EFSA: Does EFSA follow rigorous scientific standards in its activities?
- Performative aspects of EFSA's work: Does EFSA deliver effectively on its mandate?
- Procedural aspects of EFSA's work: Does EFSA follow due processes?
- Moral/ethical aspects of EFSA's work: Does EFSA protect in the public interest? Is EFSA an inclusive and transparent organisation?
- Overall credibility of EFSA's scientific work: Are the scientific outputs of EFSA authoritative? Is EFSA free from political influence?

In the remainder of this section the results of the survey are briefly introduced and discussed.

See Figure 9: The survey aimed at capturing the perceptions of stakeholders regarding the scientific and technical conduct of EFSA (see Figure 9). The statements measuring the technical character of EFSA's work included: (1) EFSA delivers scientific outputs that are of high methodological quality; (2) EFSA provides high-quality scientific advice; and (3) EFSA applies rigorous evidence selection criteria in its scientific outputs. In general, the respondents are rather positive about EFSA's scientific conduct. 74% of the respondents agree in various degrees (i.e., strongly agree/agree/somewhat agree) with the statement that EFSA delivers scientific outputs that are of high methodological quality. 67% agree that EFSA provides high-quality scientific advice and 26% of the respondents strongly agree with the statement. It is important to note that this particular statement has received the highest support from the respondents (one third strongly agree with the statement) implying that the respondents are quite positive about the quality of scientific advice that EFSA provides to EU institutions and Member States. When it comes to the claim 'EFSA applies rigorous evidence selection criteria in its scientific outputs', 70% agree with the statement, while only 17 % disagree (i.e., strongly disagree/disagree/somewhat disagree). This, in turn, indicates that the respondents are convinced and satisfied with the evidence selection practices followed by EFSA in its scientific work. In summary, the survey results overall indicate that, on average, the stakeholders of EFSA tend to have very positive perceptions of EFSA scientific/technical performance.

The respondents were also provided with the opportunity to comment on EFSA's day-to-day activities. In general, the respondents are very positive when it comes to the scientific conduct of EFSA, as illustrated in the following quote: "EFSA operates in a field with

diverse interests. Thanks to the independent scientific approach of their work EFSA is a very reliable organisation. We are impressed by their results" (Survey comment: *Representative of a national authority*).[24]

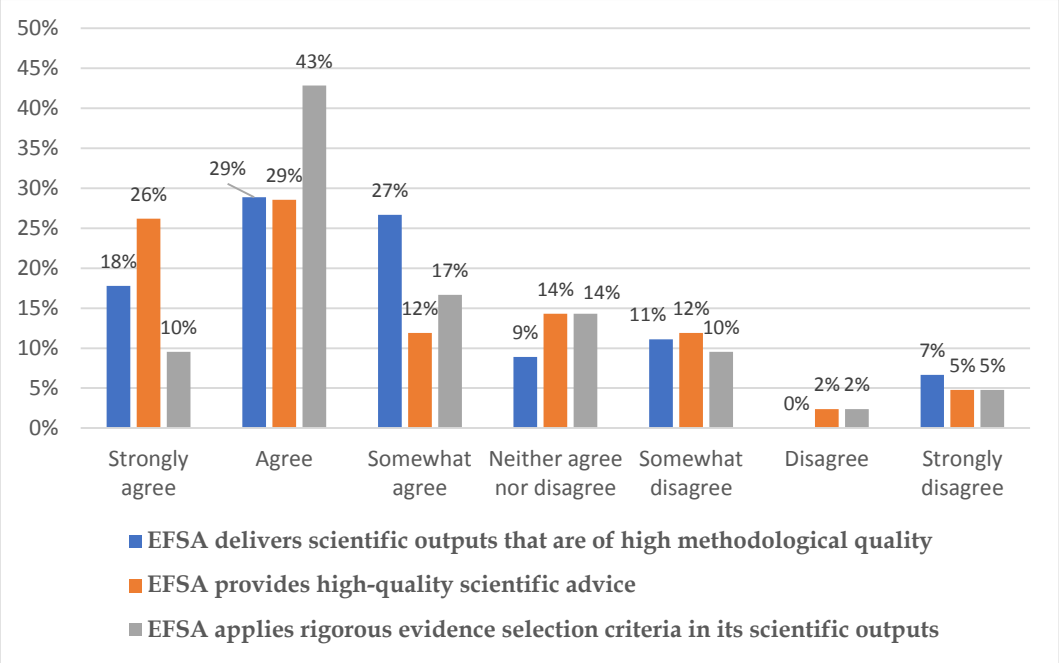

Figure 9. Opinions of the scientific/technical conduct of EFSA

See Figure 10: The survey included a question on the independence of EFSA's experts, methods and data ('EFSA is committed to safeguarding the independence of its experts, methods and data'). *Figure 10* indicates that 80% of the stakeholders who filled in the questionnaire are of the opinion that EFSA is an independent organisation, i.e. they agree with the statement on various degrees (i.e., strongly agree / agree / somewhat agree). Whereas only 9% somewhat disagree / disagree / strongly disagree with the statement. This finding is quite surprising because the desk research revealed that EFSA receives much criticism regarding its independence policies and practices. However, according to the survey results, EFSA is regarded very positively among the group of stakeholders that contributed to this survey.

On the other hand, an industry representative expressed some concerns regarding too stringent independence policies of EFSA: "strict independence policy is a blocker to the exchange of a comprehensive scientific and practical knowledge with directly involved stakeholders. We would support an adaptation of this policy to include more scientific inputs from stakeholders with a particular interest (e.g. Industry, NGOs) in a fully declared, visible and public way" (Survey comment: *industry/industry association representative*).[25]

[24] Respondents had an opportunity to provide their comments to the survey questions.

[25] Respondents had an opportunity to provide their comments to the survey questions.

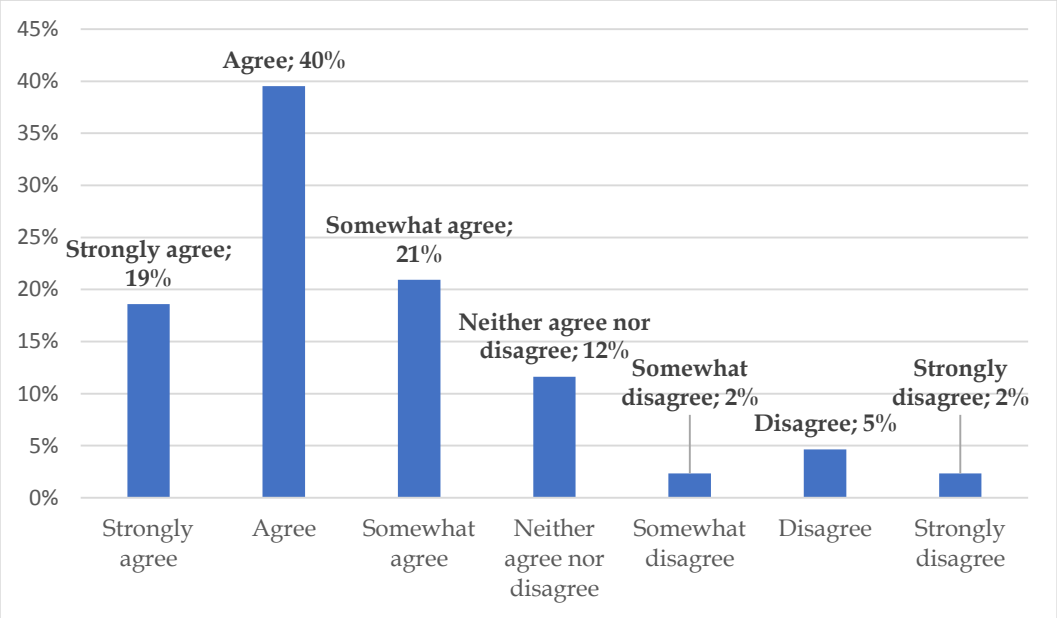

Figure 10. Perceptions about the independence of EFSA regarding its experts, methods and data

See Figure 11: Alongside the technical and scientific conduct of EFSA, the survey included questions measuring the perceptions of stakeholders regarding EFSA's organisational performance and effectiveness (see Figure 11): (1) EFSA is able to attain goals that are relevant to the organisation/stakeholder group that you belong to; (2) EFSA is capable of taking effective action in the pursuit of its core responsibilities; and (3) EFSA delivers effectively on its mandate. While the vast majority (65% - 69%) of the respondents to various degrees agree (i.e., strongly agree/agree/somewhat agree) that EFSA is able to deliver effectively in line with its mandate and core responsibilities, 14% - 19% do not believe that EFSA is an effective organisation. The vast majority of those who participated in the survey (77%) are satisfied with how EFSA attains goals that are relevant to the organisation/stakeholder group they belong to. In short, the respondents are, on average, positive regarding the performative aspects (i.e., effectiveness, ability to deliver outputs) of EFSA's conduct. However, it is important to note that 21% of the survey participants could not make up their mind (neither agreed nor disagreed) about the capability of EFSA to take effective action. This implies that the respondents found it difficult to decide if EFSA can be regarded as an assertive organisation that can take effective action in line with its mandate. The respondents of the survey suggested some reflections on this aspect of EFSA conduct: "The big problem in the regulation 1107/2009 is not the part of risk assessment, but the risk management and the enforcement of the regulation, which is not in the hands of EFSA but in the hands of the Commission and Member States. The regulatory framework we have could be improved. The problem is that the law is not enforced. Once

the risk has been assessed and determined, risk managers forget their responsibility to manage risks properly" (Survey comment: *NGO representative*).[26]

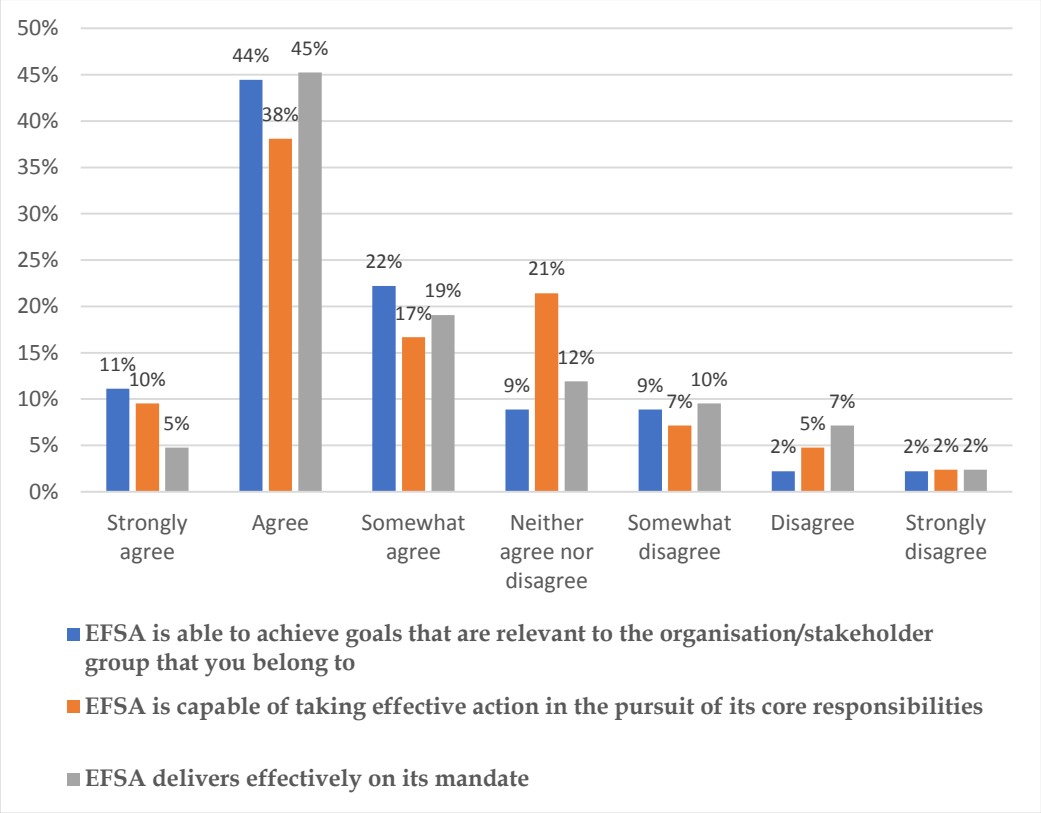

Figure 11. Opinions of the performative aspects of EFSA's work

See Figure 12: The survey included a set of questions that aims to assess the perceptions of stakeholders regarding the procedural aspects of EFSA's scientific work (see Figure 12). The statements measuring how well EFSA is capable to adhere to the proper procedures and rules include: (1) EFSA follows due process in its scientific work; (2) EFSA follows proper procedures in carrying out its scientific tasks; (3) EFSA includes legitimate stakeholders in its activities. 69% percent to various degrees agree (i.e., strongly agree / agree / somewhat agree) that EFSA follows due process in its scientific work, 73% agree with a very similar statement stating that EFSA follows proper procedures in carrying out its scientific tasks, 65% believe that EFSA is an inclusive organisation. In general, EFSA scores highly on the procedural dimension, however, 19% were hesitant (neither agreed nor disagreed) about the ability of EFSA to include stakeholders in its day-to-day activities.

[26] Respondents had an opportunity to provide their comments to the survey questions.

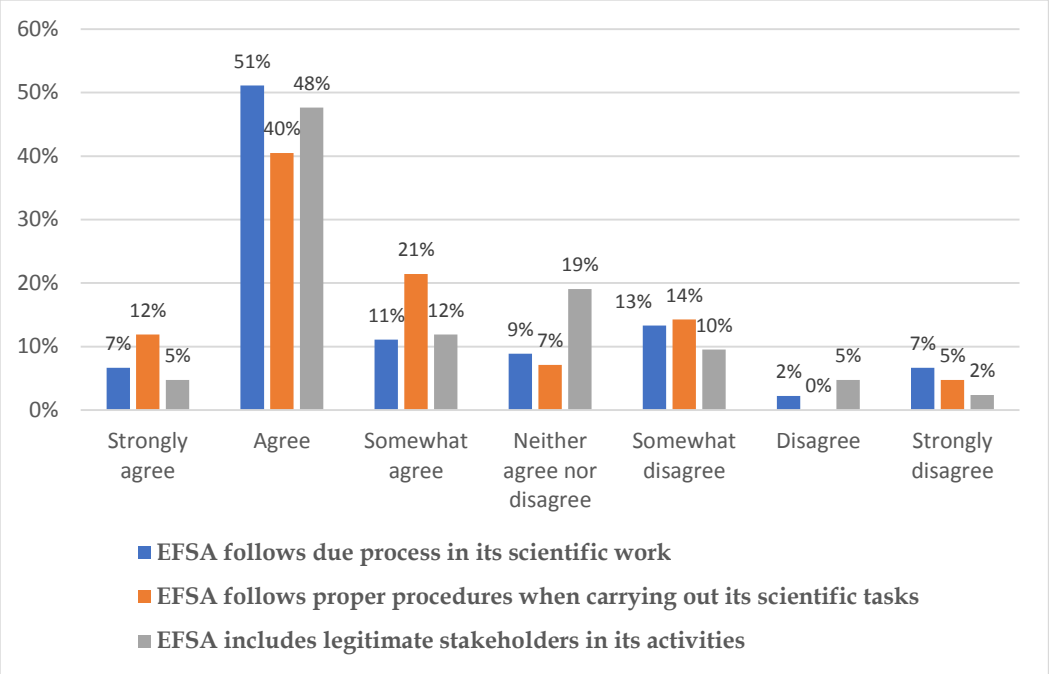

Figure 12. Opinions of the procedural aspects of EFSA's work

See Figure 13: The other group of questions aimed to assess the opinion of stakeholders regarding the moral and ethical aspects of EFSA work (see Figure 13). The moral/ethical dimension included the following statements: (1) EFSA is committed to transparency in its work; (2) EFSA is considerate towards the interests of the stakeholder group/organisation you belong to; (3) EFSA follows ethical standards in its work; and (4) EFSA protects the public interest. The desk research has indicated that EFSA received much criticism regarding its transparency practices, especially, in the context of the glyphosate case. However, the survey results indicate that the vast majority of the respondents (74%) on various degrees agree (i.e., strongly agree / agree / somewhat agree) that EFSA is a transparent organisation, whereas only 14% disagree with the statement. In a similar vein, the majority considers EFSA as an organisation that follows ethical standards (71%) and protects public interest (66%). However, EFSA received less support from the stakeholders when it comes to the statement claiming that EFSA is considerate towards the interests of the stakeholder group/organisation the respondents belong to (57% agree, whereas 33% feel that EFSA does not address their interests).

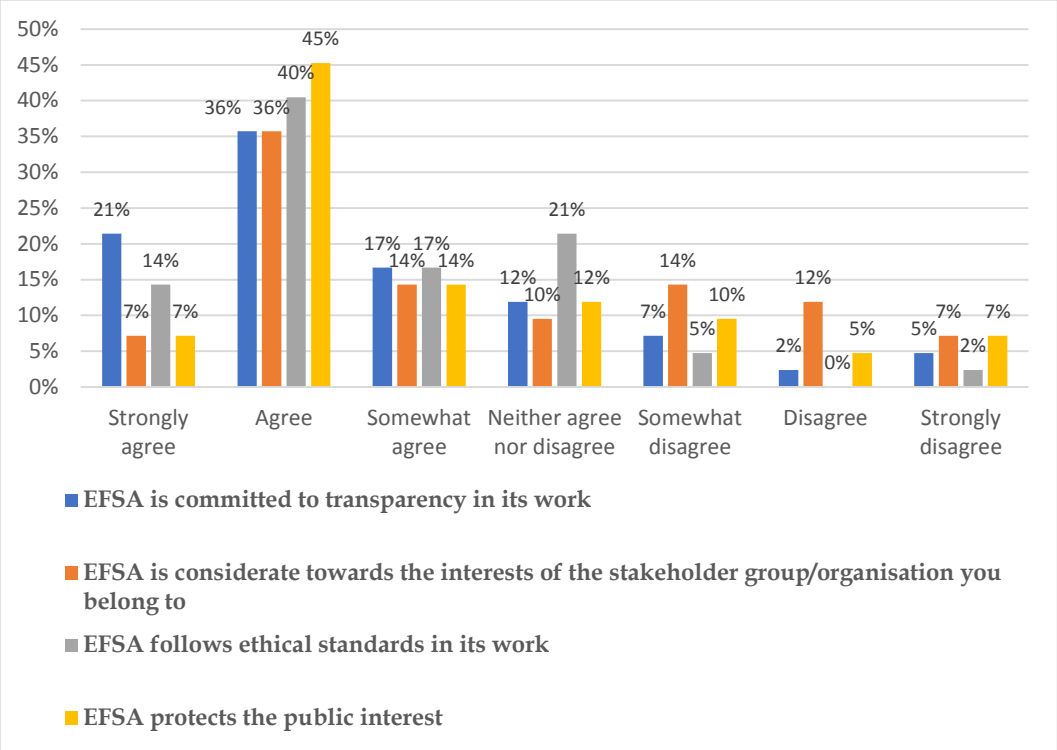

Figure 13. Opinions of EFSA moral/ethical aspects of EFSA's activities

See Figure 14: In addition to organisational reputation questions aimed at measuring scientific-technical, performative, procedural and moral aspects of EFSA scientific work, the survey also included questions that aimed to measure the credibility of EFSA (see Figure 14). Those statements included: (1) EFSA deploys consistent and predictable criteria in its scientific outputs; (2) EFSA is guided by technical as opposed to political considerations; (3) EFSA's scientific outputs are authoritative; and (4) EFSA's scientific outputs are free from political influence. Overall, EFSA is perceived as a credible organisation. The majority to various degrees agree (i.e., strongly agree / agree / somewhat agree) with the first (78%), the third statements (76%), whereas the statements claiming that EFSA is guided by technical as opposed to political considerations (67%), and the statement that EFSA's scientific outputs are free from political influence (60%) receive slightly less support from the respondents. This indicates that the respondents, to some extent, refer to the issues related to the independence of EFSA from political influence. However, they regard EFSA as an authoritative and predicable organisation. This result is not unexpected, given that the majority of the respondents (i.e., 55%) consists of the representatives of competent national authorities that work and cooperate with EFSA closely in their day-to-day activities.

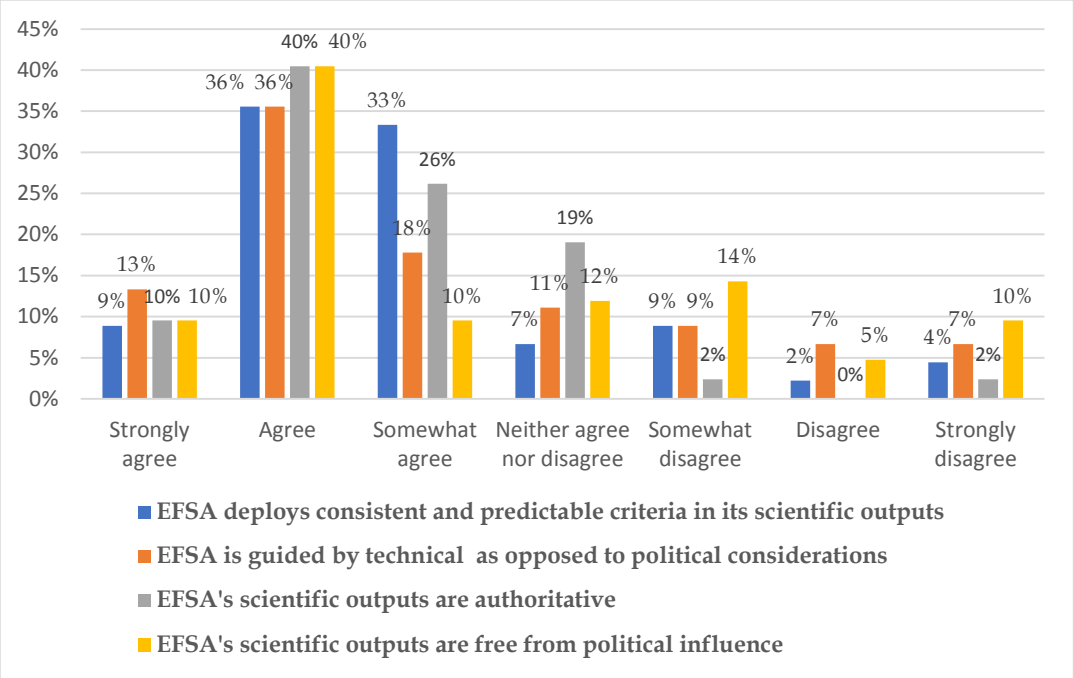

Figure 14. Credibility of EFSA

See Figure 15: The survey included a couple of questions regarding the expectations of the respondents (see Figure 15). The respondents were asked whether pesticides should be more strictly regulated in the EU (36% agree *versus* 29% disagree); whether the precautionary principle should be applied more often in the EU (41% agree *versus* 26% disagree); whether EFSA should show greater considerations for the societal implications in their scientific work (46% agree *versus* 24% disagree); whether EFSA should show greater considerations for the economic implications in their scientific work (38% agree *versus* 22% disagree); whether EFSA should be involved in risk management (28% agree versus 43% disagree). There is one clear pattern in the answers regarding the expectations of the respondents about the EU pesticides regulation practices, i.e. a considerable amount of the respondents neither agree nor disagree with the above-mentioned statements, which suggests that the respondents tend to be satisfied with the current situation (they prefer *status quo*).

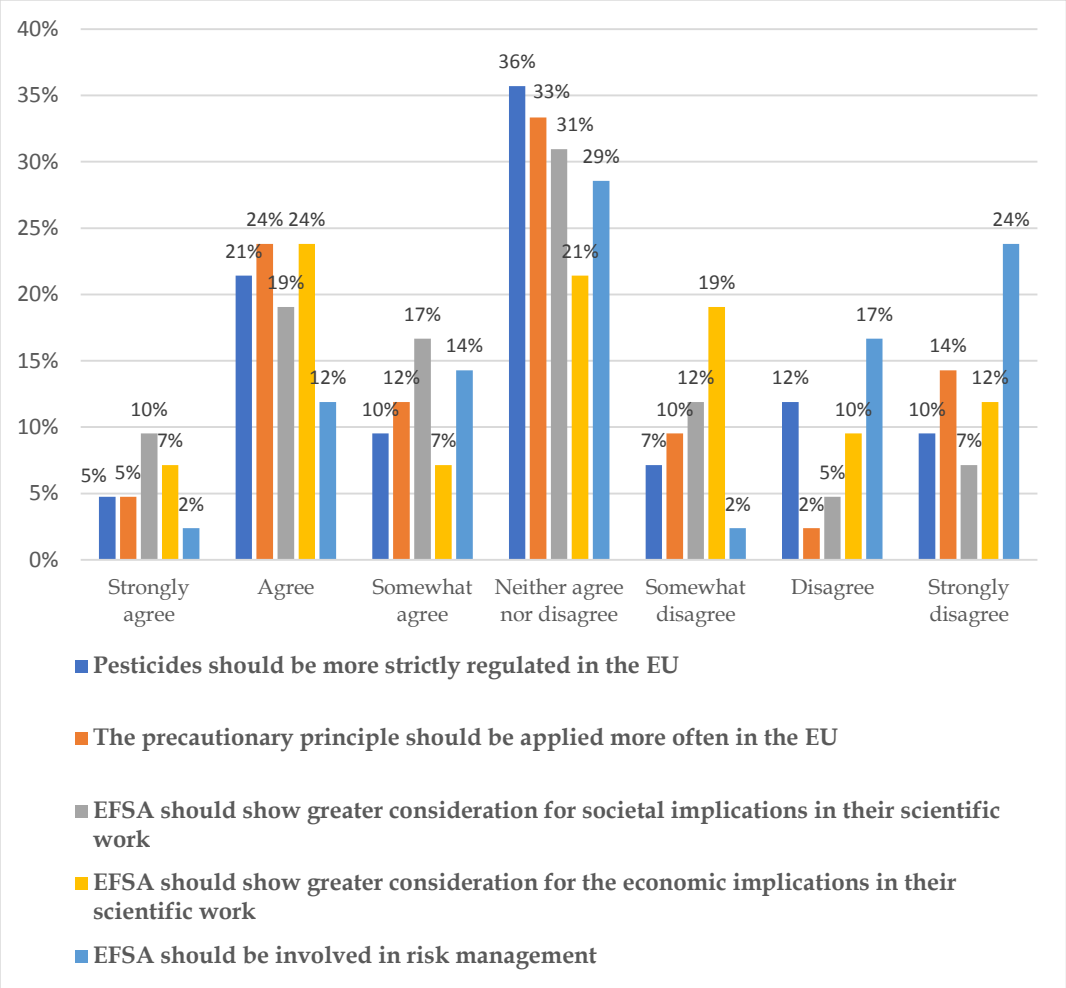

Figure 15. Expectations about pesticides regulation, precautionary principle, societal and economic impact

See Figure 16: The survey included a question on trust in EU/national institutions and agencies (see Figure 16). With this question, the researchers intended to analyse where EFSA stands in terms of trust compared to other national and EU institutions. EFSA is regarded as the most trusted institutions in the context of the organisations included in the survey (e.g. the European Commission, European Parliament). 73% of the respondents trust EFSA in various degrees (trust very much / trust / trust somewhat). In general, the respondents expressed their trust to EU agencies (72%), whereas they are less positive about the European Commission (55% replied that they trust the Commission), the European Parliament (43%), the Council of the European Union (42%).

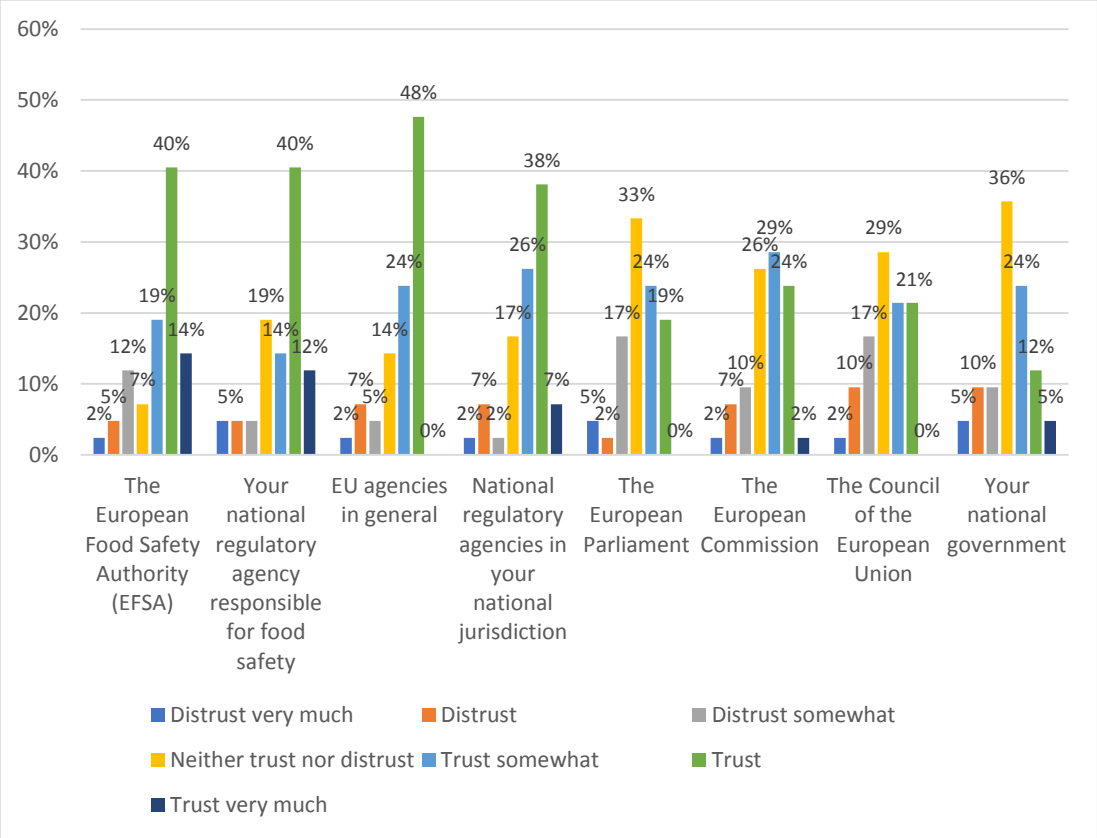

Figure 16. Trust in EU/national agencies and institutions

II – Conclusion

In order to complement the information obtained from primary document analysis and semi-structured interviews, an online stakeholders' survey was carried out to learn about stakeholders' perceptions of the scientific risk assessment model established in the EU by Regulation (EC) 1107/2009 concerning the placing of plant protection products on the market. In particular, the questions of the online survey explored the scientific/technical, procedural, performative and ethical aspects of European Food Safety Authority's (EFSA) work on risk assessments in the field of pesticides used in plant protection products.

The survey was sent to a wide range of stakeholders and organisations (research community, national regulatory authorities, NGOs, industry, etc.). It was disseminated to 293 stakeholders: including national competent authorities, health/environment NGOs and consumer groups, research community (e.g., academics), etc. The survey received 42 fully completed responses (response rate: 15%). The largest group of respondents who filled in the questionnaire is national competent authorities (55%), followed by industry/industry associations (15%) and NGOs and advocacy groups (12%), research community (8%).

The questionnaire consisted of 18 statements in which the respondents were asked to indicate the extent to which they agree or disagree (7-point Likert scale) with the statements regarding EFSA and its scientific work. The survey questions aimed to cover five different aspects of the day-to-day activities of the European Food Safety Authority: (1) technical/scientific conduct of EFSA; (2) Performative aspects of EFSA's work; (3) Procedural aspects of EFSA's work; (4) Moral/ethical aspects of EFSA's work; and (5) Overall credibility of EFSA's scientific work.

The survey results indicate that EFSA is a well-regarded organisation on various dimensions: technical/scientific, procedural, performative and ethical/moral. In particular, the scientific/technical aspects of its daily conduct are perceived rather positively by the stakeholders who have submitted their contributions to the survey. Furthermore, the respondents perceive EFSA as a credible agency whose work is authoritative and free from the political influence. The survey indicated that EFSA is regarded as a transparent, trustworthy and independent organisation.

However, the results of this survey have to be interpreted carefully. First, there might be a self-selection bias, e.g. only stakeholders that are positive about EFSA filled in the questionnaire. Second, even though the researchers of this study attempted to be as exhaustive as possible and send the questionnaire to an extensive list of EFSA stakeholders, an exhaustive list of stakeholders does not exist. For this reason, only a small sample of stakeholders was surveyed. Furthermore, as the population of stakeholders is not known, it is difficult to assess how representative the surveyed sample is to the actual population of EFSA stakeholders. Third, the majority (55%) of those who filled in the questionnaire consists of the representatives of competent national authorities. As a result, one might expect opinions that are skewed towards more positive perceptions about EFSA and its scientific work. Fourth, as the survey received only 42 responses, it is difficult to capture statistically significant differences between various stakeholder groups (competent authorities, health/environment NGOs and consumer groups, research community, industry and industry associations).

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Annex I: List of interviews

Table 5. List of interviews

Number/reference in the text	Interviewee	Date	Duaration of the interview
1. ECHA representative #1	Representative of ECHA (1 interviewee)	07/12/2018	01:07:22
2. EFSA representative #2	Representative of EFSA (1 interviewee)	19/02/2018	01:02:45
3. BfR representative #3	Representative of BfR (German competent authority) (1 interviewee)	27/02/2018	01:24:41
4. BVL representatives #4	Representative of BVL (German competent authority) (3 interviewees)	28/02/2018	00:51:35
5. ANSES representatives #5	Representatives of ANSES (4 interviewees)	20/03/2018	01:06:57
6. APVMA representatives #6	Representatives of APVMA (Australian regulatory authority) (3 interviewees)	27/03/2018	00:45:00
7. US EPA representatives #7	Representaive of US EPA	06/04/2018	Written responses

Regulation (EC) 1107/2009 lays down the main instruments for placing effective plant protection products (using pesticide substances) on the market that are safe for humans, animals and the environment, while at the same time ensuring effective functioning of the internal market and improved agricultural production.

This European Implementation Assessment found that the above objectives, while largely relevant to real needs, are not being achieved in practice. In particular, implementation of the main instruments of the regulation – substance approval, plant protection products authorisation and enforcement of the regulatory decisions taken in the frame of the approvals and authorisations, is problematic, which also affect other related EU policies.

Nevertheless, despite the implementation challenges observed, stakeholders – including national competent authorities, health/environment NGOs, manufacturers of substances and plant protection products and their users (farmers) – agree that the EU is the appropriate level at which regulatory action in the field of pesticides (used in plant protection products) should continue to take place.

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