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Centre Suisse de Toxicologie Humaine Appliquée  
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# **Combination (“cocktail”) effects of pesticide residues in food**

**SCAHT report for FSVO**

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## Abbreviations

ADI	Acceptable Daily Intake
ALARA	As Low As Reasonably Achievable
ANSES	French Agency for Food, Environmental and Occupational Health and Safety
AOP	Adverse Outcome Pathways
ARfD	Acute Reference Dose
ATSDR	U.S. Agency for Toxic Substances and Disease Registry
BfR	German Federal Institute for Risk Assessment
BMD	Benchmark Dose
BMEF	German Federal Ministry of Food and Agriculture
BPR	Biocide Products Regulation
CAG	Cumulative Assessment Group
CAT	Category
ChemRRV	Chemical Risk Reduction Ordinance (Chemikalien-Risikoreduktions-Verordnung)
ChemV	Chemicals Ordinance (Chemikalienverordnung)
CLP	Classification, Labelling and Packaging
CMG	Common Mechanism Group
CMR	Carcinogenic, mutagenic, reprotoxic
CRI	Cumulative Risk Index
EC	European Commission
ECHA	European Chemicals Agency
EEA	European Environment Agency
EFSA	European Food Safety Authority
EMA	European Medicines Agency
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FOAG	Swiss Federal Office for Agriculture (BLW, OFAG)
FOEN	Swiss Federal Office for the Environment (BAFU, OFEV)
FOPH	Federal Office of Public Health (BAG, OFSP)
FQPA	U.S. Food Quality Protection Act
FSVO	Swiss Federal Food Safety and Veterinary Office
GAP	Good Agricultural Practice
GHS	Globally Harmonized System
HESI	Health and Environmental Science Institute
HI	Hazard Index

HQ	Hazard Quotient
IPCS	International Programme on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
JRC	Joint Research Centre of the European Commission
INSERM	French National Institute of Health and Medical Research
LOAEL	Lowest Observed Adverse Effect Level
LOD	Limit of Detection
MoA	Mode of Action
MCR	Maximum Cumulative Ratio
MCRA	Monte Carlo Risk Assessment
MRL	Maximum Residue Level
NFUP	National Program for Foreign Substance Detection
NOEL	No Observed Effect Level
NOAEL	No Observed Adverse Effect Level
OECD	Organization for Economic Cooperation and Development
PBTK	Physiologically-based toxicokinetic (model or modeling)
PSMV	Plant Protection Products Ordinance (Pflanzenschutzmittelverordnung)
PPP	Plant Protection Products
PPPR	Plant Protection Products Regulation
RASFF	EU Rapid Alert System for Food and Feed
REACH	EU Regulation on Registration, Evaluation, Authorization and Restriction of Chemicals
RfPI	Reference Point Index
RIVM	Dutch National Institute for Public Health and the Environment
RPF	Relative Potency Factor
SCCS	EU Scientific Committee on Consumer Safety
SCHEER	EU Scientific Committee on Health, Environmental and Emerging Risks
SECO	State Secretariat for Economic Affairs
TD	Toxicodynamic
TEF	Toxic Equivalency Factor
TK	Toxicokinetic
TTC	Threshold of toxicological concern
TWI	Tolerable Weekly Intake
USEPA	U.S. Environmental Protection Agency
VPRH	Pesticide Residues Ordinance (Verordnung über Pestizidrückstände)
WHO	World Health Organization

## Executive summary

### Zusammenfassung

#### **Hintergrund und gesetzliche Bestimmungen**

Die Bevölkerung kann im Alltag gleichzeitig gegenüber zahlreichen Pestizindrückständen aus der Umwelt sowie aus Lebensmitteln und Getränken exponiert sein. Es bestehen Bedenken, dass bei einer Kombination solcher Rückstände unterschiedliche und nur schwer vorhersehbare Wirkungen - sogenannte «Cocktail-Effekte» - auftreten könnten. Die Einschätzung der damit verbundenen Risiken für die menschliche Gesundheit kann entsprechend anders ausfallen als für die einzelnen Substanzen.

Angesichts der aktuellen wissenschaftlichen und regulatorischen Entwicklungen auf europäischer und internationaler Ebene wurde das Schweizerische Zentrum für Angewandte Humantoxikologie (SCAHT) vom Bundesamt für Lebensmittelsicherheit und Veterinärwesen (BLV) beauftragt, die Bewertungsmethodik und die Hinweise auf Kombinationswirkungen verschiedener Rückstände aus Pflanzenschutzmitteln (PSM) zu prüfen. Der Bericht ist aus Schweizer Perspektive verfasst und soll eine Übersicht zu den Akteuren geben, die an der Marktregulierung von PSM, an der Durchführung von Risikobewertungen, an der Festlegung von Höchstwerten für Pestizindrückstände sowie an der Planung und Durchführung von Lebensmittelkontrollen beteiligt sind. Er stützt sich hauptsächlich auf die Lebensmittelgesetzgebung der Schweiz und der EU, berücksichtigt aber auch andere relevante Bestimmungen zu den kumulativen Effekten von Pestizidmischungen in anderen Gesetzesstexten über Chemikalien. Der Bericht ist in Form von Fragen und Antworten aufgebaut, was die Risikokommunikation im Zusammenhang mit diesem Thema erleichtern soll.

#### **Weshalb ist die Toxizität von Mischungen für den bisher verwendeten regulatorischen Ansatz zur Risikobewertung von chemischen Substanzen eine Herausforderung?**

Das Verhalten von chemischen Mischungen zu verstehen, ist komplex, weil es fast unendlich viele mögliche Kombinationen gibt. Diese ändern sich im Laufe der Zeit ständig in ihren Zusammensetzungen und Konzentrationen, ihren toxikologischen Eigenschaften sowie der Dauer und Häufigkeitsmuster der Exposition, aber auch je nach den Stoffwechselmerkmalen der jeweiligen Person. Es wurden Bedenken über die Grenzen der geltenden Regulierungen geäussert, die den Fokus auf die individuelle Bewertung der einzelnen Stoffe legen. Spezifische Bestimmungen zu den Kombinationseffekten von chemischen Mischungen (einschliesslich Pestizide) bestehen bereits in verschiedenen Chemikalien- und Lebensmittelgesetzen der EU und der Schweiz, doch die Methoden zur Risikobewertung für solche Mischungen befinden sich noch im Entwicklungsstadium und sind noch kein etablierter Bestandteil der Regulierungsverfahren der EU. Diese Unzulänglichkeiten sind seit Längerem bekannt, ebenso wie die Notwendigkeit, wissenschaftliche und regulatorische Schritte mit dem Ziel einzuleiten, neuartige Toxizitätstest-Strategien sowie Prognosemethoden zur Einschätzung der Gefahren und Risiken von chemischen Mischungen zu entwickeln. Zentral bei der Umsetzung dieser Ziele sind eine verstärkte sektorübergreifende, technische Vereinheitlichung und eine Harmonisierung im Umgang mit Aspekten wie Terminologie sowie der Verfahren zur Generierung, zum Sammeln und zur Weitergabe von Daten und der Anforderungen an die Tests zur Bewertung der Sicherheit von chemischen Mischungen (einschliesslich Pestizide). Alle diese wissenschaftlichen und regulatorischen Themen zu behandeln ist ein langer Prozess, doch die Entwicklung der entsprechenden Verfahren und Methoden ist derzeit im Gange.

#### **Welche Anstrengungen laufen derzeit in Wissenschaft und Politik zur Bewältigung dieser Herausforderungen?**

Entsprechende Schritte wurden bereits eingeleitet, sowohl auf wissenschaftlicher als auch auf regulatorischer Ebene, in Form von nationalen und internationalen, multisektoriellen Forschungs-

programmen unter Einbezug aller Interessensgruppen sowie durch regulatorische Initiativen zur Bewältigung der Herausforderungen in der Risikobewertung von chemischen Mischungen und zur Bestimmung verbleibender Lücken in der Erforschung von Cocktail-Effekten sowie zur Festlegung der Politik und der künftigen Prioritäten für dieses Thema. Explizite rechtliche Anforderungen zur Bewältigung der kumulativen und synergistischen von Mischungen wurden in verschiedenen Gesetzestexten der EU und der Schweiz für Chemikalien, Pestizide und Biozide eingeführt. Auf EU-Ebene und international sind intensive Bemühungen im Gange und geplant, die darauf abzielen, neue Ansätze, Werkzeuge und Methoden zu entwickeln, um die potenziellen Effekte von chemischen Mischungen auf die Gesundheit von Mensch und Tier sowie auf die Umwelt besser behandeln zu können. Aus den Empfehlungen der Europäischen Kommission zur Festlegung von Forschungs- und Regulierungsschwerpunkten ist eine entsprechende Wissenschafts- und Politikagenda hervorgegangen. Strategien für einen nachhaltigen Einsatz von Pflanzenschutzmitteln mit möglichst geringen Auswirkungen auf die menschliche Gesundheit und die Umwelt sowie die Förderung einer integrierten Schädlingsbekämpfung wurden in der EU und der Schweiz bereits umgesetzt, auch durch Regulierungen. Dies trägt zur Reduktion der Menge und der potenziellen gesundheitlichen Auswirkungen infolge von Spuren mehrerer Pestizidrückstände in Lebensmitteln und Trinkwasser bei.

***Welche Hinweise bestehen für toxische Kombinationswirkungen von chemischen Mischungen (einschliesslich Pestizide)?***

Unter gewissen Bedingungen können Chemikalien in einer Mischung kombiniert so wirken, dass dies die Gesamttoxizität beeinflusst, womit sich das Risiko für schädliche Wirkungen verändern kann. Im Wesentlichen lassen sich drei Kombinationseffekte unterscheiden: additive, synergistische und antagonistische Effekte. Chemikalien können auf eine nicht-interaktive Weise durch eine ähnliche Wirkungsweise (Dosisadditionsmodell) oder durch unterschiedliche Wirkungsweisen zusammenwirken (Wirkungsadditionsmodell) oder sie können ihre Wirkung gegenseitig durch synergistische (verstärkende) oder antagonistische (abschwächende) Mechanismen beeinflussen (Wechselwirkungsmodell). Dosisaddition und Wirkungsaddition sind vermutlich für die Mehrheit toxischer Kombinationseffekte von chemischen Mischungen verantwortlich und wurden für die Risikobewertung als Standardannahme vorgeschlagen. Synergistische Effekte scheinen selten und hauptsächlich bei hohen Dosen aufzutreten, und im Allgemeinen wird davon ausgegangen, dass die Wahrscheinlichkeit von synergistischen Effekten durch Mehrfachpestizidrückstände in Lebensmitteln bei Dosen, die über die Ernährung aufgenommen werden, gering ist.

***Welche Konzentrationen von Pestizidrückständen enthalten unsere Lebensmittel?***

Überwachungsstudien in der Schweiz und Europa zeigen, dass die Pestizidrückstände, die in und auf unseren Lebensmitteln verbleiben, im Allgemeinen nur geringe Konzentrationen erreichen. Die amtlichen Kontrollen haben ergeben, dass in der Schweiz hergestellte tierische und pflanzliche Lebensmittel die regulatorischen Anforderungen erfüllen und deren Konsum unbedenklich ist. Gemäss den Ergebnissen der 2015 und 2016 durchgeföhrten gesamtschweizerischen Programme und Kampagnen enthielten 98% bzw. 99% der Proben von Lebensmitteln tierischer und pflanzlicher Herkunft keine Pestizid-Rückstände oder nur in Konzentrationen innerhalb der gesetzlichen Höchstgehalte. Hingegen werden in Lebensmitteln aus Nicht-EU-Ländern von Zeit zu Zeit erhöhte Konzentrationen von Pestizidrückständen gefunden. Das BLV hat Massnahmen getroffen, um die Grenzkontrollen ab dem 1. Mai 2020 zu verstärken. Bedenken der Öffentlichkeit über die Qualität der Lebensmittel und des Trinkwassers haben dazu geführt, dass mehr Überprüfungen, Überwachungen und Kontrollen durch die Lebensmittelsicherheitsbehörden durchgeföhrt werden. Die Lebensmittelsicherheitsbehörden verbessern kontinuierlich die Probenahmen und das Monitoring für Pestizidrückstände in Lebens- und Futtermitteln, um neuen Herausforderungen, Bedrohungen und Bedenken in der Öffentlichkeit gerecht zu werden.

### **Wie hoch ist die Belastung der Bevölkerung gegenüber Pestizindrückständen im Allgemeinen?**

Eine Exposition der allgemeinen Bevölkerung gegenüber Pestizindrückständen tritt hauptsächlich über die Ernährung auf (einschliesslich Trinkwasser). Eine Exposition ist ausserdem möglich beim Umgang mit Pflanzenschutzmitteln (Anwendung, Lagerung, Entsorgung), bei Freizeitaktivitäten wie Gartenarbeit oder per Zufall durch Pestizidabdrift wenn sich jemand während und direkt nach der Verwendung von PSM in unmittelbarer Nähe aufhält (Passanten) oder in der Nähe von Landwirtschaftsflächen lebt (Anwohner). Zu bestimmen und vorherzusehen, welcher Art von Pestizidmischungen eine Bevölkerung oder eine Einzelperson ausgesetzt sein wird, ist schwierig, weil sich die Belastungen durch zufällige Mischungen von Pestiziden ständig in ihrer Kombination und Konzentration ändern. Die Exposition variiert je nach Person, unter anderem aufgrund von deren Aktivitäten, Beruf, Wohnort und Konsumgewohnheiten. Ausserdem reduzieren sich normalerweise die Pestizindrückstände von Lebensmitteln im Laufe der Lagerung, Aufbereitung (z.B. Waschen, Schälen), der industriellen Verarbeitung und der Zubereitung von Lebensmitteln.

### **Worin liegen die gesundheitlichen Risiken im Zusammenhang mit Mehrfachbelastungen durch Pestizindrückstände in der Ernährung?**

Pestizide haben ausgeprägte chemische und biologische Eigenschaften und sind deshalb streng reguliert. Die Lebensmittelgesetzgebung in der Schweiz und in Europa hält explizit fest, dass Pestizindrückstände keine schädlichen Wirkungen auf Menschen haben dürfen – auch keine kumulativen und synergistischen Effekte. Die für die Lebensmittelsicherheit zuständigen Behörden sind für die Konsumentensicherheit und die Beurteilung des potentiellen Gesundheitsrisikos zuständig, das von Pestiziden in der Ernährung ausgeht. Sie berücksichtigen dabei sowohl die Toxizität der einzelnen Substanz (Gefahr) als auch die für die einzelnen Lebensmittel und verschiedene Ernährungsgewohnheiten der Bevölkerung zu erwartenden maximalen Pestizidwerte (Exposition). Konsumentinnen und Konsumenten können sehr geringen Mehrfachpestizindrückständen durch den Konsum von Lebensmitteln und Trinkwasser ausgesetzt sein. Der aktuelle Konsens geht davon aus, dass synergistische Effekte im Rahmen der Ernährung üblicherweise nicht auftreten. Gemäss den verfügbaren wissenschaftlichen Daten ist es unwahrscheinlich, dass die mit der Ernährung aufgenommenen Pestizindrückstandsmischungen für den Menschen ein inakzeptables Gesundheitsrisiko darstellen, vorausgesetzt, dass die einzelnen Komponenten dieser Mischungen auf der Grundlage der etablierten Risikobewertungsansätze angemessen reguliert sind. Je nach Ernährungsgewohnheiten können Personen jedoch erhöhten Pestizindrückständen ausgesetzt sein, wie sie in gewissen Fällen bei importierten Lebensmitteln aus Nicht-EU-Ländern festgestellt wurden, die ein Gesundheitsrisiko darstellen können. Insgesamt ist das Gesundheitsrisiko, das für Konsumenten von Pestizindrückständen in Lebensmitteln und Trinkwasser ausgeht, jedoch nach wie vor gering: diese Meinung vertreten alle wichtigen Behörden für Lebensmittelsicherheit weltweit und auch das BLV.

### **Weshalb bedeutet die Überschreitung eines Pestizidhöchstwerts nicht automatisch ein Gesundheitsrisiko?**

Die als Rückstandshöchstwerte festgelegten Konzentrationen in Lebens- und Futtermitteln müssen so gering wie technisch machbar und für die Konsumentinnen und Konsumenten unbedenklich sein. Zur Erreichung dieses Ziels werden die Rückstandshöchstwerte gemäss der Guten Landwirtschaftlichen Praxis so tief wie möglich festgesetzt. Rückstandshöchstwerte sind technisch gesehen Konzentrationswerte in Lebensmitteln und rechtlich gesehen internationale Handelsstandards. Die Rückstandshöchstwerte sind klar zu unterscheiden von gesundheitlichen Empfehlungswerten wie dem Acceptable Daily Intake (Erlaubte Tagesdosis), die angeben, welche Höchstdosen eine Person ohne Gesundheitsrisiko aufnehmen darf. Die Exposition wird berechnet, indem der Rückstandshöchstwert mit der Menge des entsprechenden konsumierten Lebensmittels multipliziert wird, und solange die Belastung unter der erlaubten Tagesdosis bleibt, ist dies unbedenklich. In den meisten Fällen werden die Rückstandshöchstwerte weit unter dem Wert

angesetzt, der aus toxikologischer Sicht akzeptabel wäre. Deshalb stellt das Überschreiten der Höchstwerte bei Pestizidrückständen in Pflanzen zwar einen Verstoss gegen die Handelsnormen dar, es bedeutet aber nicht automatisch ein Gesundheitsrisiko für den Menschen. Falls die für Lebensmittelsicherheit zuständigen Behörden für eine Konsumentengruppe ein Risiko feststellen, setzen sie die Rückstandshöchstwerte tiefer an, oder sie verbieten die Verwendung eines Pestizids in einer bestimmten Pflanzenkultur.

Zitieren als: Roth N., Wilks MF. Kombinationswirkungen von Pestizidrückständen in Lebensmitteln. Zusammenfassung. Bericht für Bundesamt für Lebensmittelsicherheit und Veterinärwesen (BLV). Schweizerisches Zentrum für Angewandte Humantoxikologie (SCAHT), Basel, 6. November 2018.

### **Disclaimer**

The present report reflects the views of the Swiss Centre for Applied Human Toxicology (SCAHT) only and does not necessarily reflect the official position of the Swiss Federal Food Safety and Veterinary Office (FSVO).

## 1 Introduction

### 1.1 Background and terms of reference

Real-life exposure of the general population to pesticide residues may simultaneously involve multiple substances from multiple exposure sources, such as the environment, food and beverages. Concern has been expressed that adverse effects from such combinations, also known as 'cocktail effects', may occur in different and potentially unpredictable ways, thus leading to a change in the risk to human health when compared to that resulting from exposure to the individual substances.

At a joint meeting on 8<sup>th</sup> January 2018 between the Swiss Centre for Applied Human Toxicology (SCAHT) and the Swiss Federal Food Safety and Veterinary Office (FSVO), SCAHT was requested to review the methodology for assessing and the evidence for combination effects of mixtures of pesticide residues in food, in the light of recent scientific and regulatory developments at EU and international level. The report shall be used for external communication to the media and the public. The report shall take the Swiss Food Laws as main reference point, and shall cover at least the following:

- *What is the state of the science to support the concept of 'cocktail effects', with a focus on the toxicity of mixtures of plant protection products residues in food;*
- *What are the methods and tools currently in use for assessing human health hazards and risks of pesticide mixtures;*
- *What are the regulatory requirements for taking cumulative effects of pesticide mixtures into account, including state of play at EU and international level;*
- *What is known about current human exposure to mixtures of plant protection product residues, including consideration of the relevant sources, food monitoring and analysis, and the setting of maximum residue limits levels;*
- *What are the potential human health risks resulting from exposure to mixtures of plant protection product residues in the diet, with a consideration of specific target groups in the general population;*
- *What are the areas of uncertainty and the existing gaps with the science and the regulation of plant protection products and their residues in food, including needs for action.*

### 1.2 Structure of the report

The present report focuses on the current state of the science and regulatory state of play in relation to the assessment of hazards and health risks from mixtures of pesticide residues in food as a consequence of their use in plant protection products (PPPs). In doing so, it takes a Swiss perspective, aiming at mapping the different actors involved in regulating plant protection products, conducting risk assessment activities and setting maximum limits for pesticide residues, as well as planning and executing food controls. While taking the Swiss/EU Food laws as main reference points, the report also considers other relevant legal provisions on cumulative and synergistic effects of pesticide mixtures in other pieces of chemical legislation. Hazards, exposure and potential health risks from mixtures of PPPs are also discussed in the wider context of chemical and pesticide regulations, taking a historical, regulatory and scientific perspective.

- In section 2, key definitions and concepts used throughout the report are presented. Related topics such as '*endocrine disruption*' or '*low dose effects*', which are often encountered in the scientific and regulatory literature when discussing potential health risks of mixtures of PPP residues, are also addressed for clarification;

- Section 3 gives general background information on the regulation and risk assessment of PPP mixtures and their residues in food, incl. historical developments, and current scientific and regulatory challenges, from a Swiss and international perspective;
- Hazards, exposure and health risks from mixtures of PPP residues in the dietary context are covered in sections 4, 5 and 6, respectively.

The report is structured in a *question and answer* (Q&A) format to facilitate risk communication on the topic, and compiles a list of frequently discussed items in the public arena. The Q&As are organized into sections and subsections in a progressive fashion (i.e. starting with sections on definitions, regulation, hazard, exposure and risk), that can be read either in a linear or non-linear way. Cross-references are made to facilitate navigation across the various topics addressed in the report. Numerous footnotes and links provide more details on particular aspects. A glossary of the terms used throughout the report is provided at the end of the report.

### 1.3 Methodology used

A rapid (non-systematic) scoping of the internet was conducted in January 2018 using google as search engine to clarify how cocktail effects of pesticides are discussed in the public and regulatory arena: (i) in the media, to identify main public concerns; (ii) by scientific and governmental bodies, to identify regulatory status, position statements, and risk communication on the topic. The outcome of the scoping exercise was used to support the development of a list of key questions to be addressed in the report (see **Appendix I**).

When conducting a literature search, SCAHT gives preference to: (i) scientific publications in the peer-reviewed literature; (ii) public-access documents in the "grey literature", i.e. from vetted sources such as regulatory agencies and other government bodies or related scientific organizations which benefit from an internal peer-review process by panels of experts, e.g. the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), the European Food Safety Authority (EFSA), and the World Health Organization (WHO), as well as the EU non-food Scientific Committees (SCCS, SCHEER) and major EU Member States Health Authorities such as the German Institute for Risk Assessment (BfR) or the Dutch National Institute for Public Health and the Environment (RIVM).

### 1.4 Terminology used

Various terms have been proposed in the US and EU to describe the risks resulting from simultaneous or sequential exposure to two or more different chemicals via common or different routes of exposure from common or different sources. In the US, the regulatory assessment of risks from exposure to multiple chemicals is referred to as '*cumulative risk assessment*'. This terminology has been adopted in the EU in the recent years in some documents on mixture risk assessment from public institutions (e.g. EFSA, 2007) or scientific organization (e.g. HESI RISK21 project; Solomon et al., 2016; Moretto et al., 2017). The term '*cumulative*' is also used in some parts of the EU chemical legislation for the risk assessment of a single chemical following multiple exposure from different sources and/or via different routes. In the US, this situation has been termed '*aggregate*' exposure to a single chemical, in contrast to a '*cumulative*' exposure to multiple chemicals (see **Table 1**).

This situation has led to confusions, calling for more standardisation and harmonisation at international level. The inclusion of the terms '*aggregate exposure*', '*aggregate dose*', '*cumulative exposure*', and '*cumulative dose*' in the International Programme on Chemical Safety (IPCS) glossary has been postponed, awaiting

further developments in the field (WHO/IPCS, 2004), and recommendations on the topic have been issued (WHO/IPCS, 2009a) (see **Table 1**).

The general term '*mixture risk assessment*' is used throughout this document to avoid any terminological confusions. Substances grouped together for evaluation of combined exposure are referenced as an '*assessment group*', according to the WHO/IPCS (2009a) recommendations.

**Table 1: Terminology variations for addressing combined exposure to chemical mixtures**

(Sources: Meek et al., 2011; Kienzler et al., 2016; WHO/IPCS, 2009a)

Chemical mixture	Exposure route	Assessment type EU	Assessment type US	Assessment type WHO
Single chemical	All routes <sup>a</sup>	Cumulative	Aggregate	Aggregate <sup>d</sup>
Multiple chemicals	Single route	? <sup>b</sup>	? <sup>b</sup>	Cumulative <sup>d</sup>
Multiple chemicals	All routes <sup>a</sup>	Mixture <sup>c</sup>	Cumulative	Cumulative <sup>d</sup>

<sup>a</sup>Refers to the exposure from multiple sources and by multiple pathways and routes.

<sup>b</sup>It is recommended by the WHO/IPCS (2009a) that exposure to "multiple chemicals by a single route" be distinguished from exposure to "multiple chemicals by multiple routes", and use "combined exposure to multiple chemicals". However, no specific reference is made in the EU and US jurisdictions regarding the terminology to be used for this specific type of assessment.

<sup>c</sup>REACH and CLP use the term 'mixture' for a 'mix or solution of two or more substances'.

<sup>d</sup>WHO/IPCS recommends to refer to: (i) aggregate exposure in case of exposure to a single chemical from multiple sources and by multiple pathways and routes; and (ii) combined exposure in case of exposure to multiple chemicals by a single route and exposure to multiple chemicals by multiple routes (sometimes referred to as 'cumulative exposure').

## 2 Some key concepts and definitions

The following section defines key terms and concepts that are referred to in the report, such as '*pesticides*', '*plant protection products*', '*residues*', '*chemical mixture*', and '*cocktail effect*'. When evaluating the potential health risks from dietary exposure to mixtures of pesticide residues, other concepts such as '*endocrine disruption*' or '*low dose effects*' are often encountered in the scientific and regulatory literature. These concepts are *not* an *intrinsic* part of cocktail effects or chemical mixtures. Since it appears that all these concepts are regularly mixed up in the public and media discourse, their definitions are presented hereafter for clarification.

### 2.1 Pesticides

#### 2.1.1 What are pesticides?

According to the Swiss VPRH<sup>1</sup> and EU Regulation 396/2005<sup>2</sup>, '*pesticides*' are active substances, metabolites and/or breakdown or reaction products of active substances which are currently or formerly used in plant protection products (PPPs). Pesticides aim to prevent, control or kill a harmful organism ('pest') or a disease. Pesticides are most commonly used as plant protection products (see below) to protect plants or plant products during production, storage and transport. The term '*pesticide*' also includes biocidal active substances which are used for non-agricultural purposes (e.g. included in preservatives and disinfection agents).

#### 2.1.2 What is a plant protection product?

By definition, a plant protection product (PPP) is the formulation of active pesticidal ingredients (used for agricultural purposes) and co-formulants (see also below).

*Nota Bene: the terms 'pesticides' and 'plant protection products' are sometimes used as synonyms. In practice, a distinction is made between pesticides that are intended for crop/plant uses before or after harvest, i.e. PPPs, and pesticides for non-crop/non-plant uses, i.e. biocides.*

#### 2.1.3 What is an active substance?

A plant protection product (PPP) usually contains one or more principal components, so-called '*active substances*' (or '*active ingredients*'), that are responsible to specifically combat pests and/or plant diseases. An active substance can be either chemical (incl. pheromones), biological (e.g. a microorganism) or both (e.g. a plant extract). These substances have often potent biological activity against target organisms that could potentially elicit adverse effects on non-target organisms (e.g. fish, bees) and humans.

#### 2.1.4 What is a co-formulant?

In addition to the '*active substance*', a plant protection product usually contains so-called '*co-formulants*' (sometimes referred to as '*inert ingredients*' in the literature), that are mixed in order to influence the properties of the plant protection product in a targeted manner; they are used to facilitate the application of the product (e.g. '*anti-foaming*' agents) or for their solvent properties, or to increase effectiveness ('*synergists*'), or increase selectivity and plant safety ('*safeners*'), in order to achieve the same effect with

<sup>1</sup> SR 817.021.23. Verordnung des EDI über die Höchstgehalte für Pestizidrückstände in oder auf Erzeugnissen pflanzlicher und tierischer Herkunft (Verordnung über Pestizidrückstände, VPRH) vom 16. Dezember 2016 (Stand am 1. Mai 2018).

<sup>2</sup> Regulation (EC) No 396/2005 of the European Parliament and of the Council of 23 February 2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin and amending Council Directive 91/414/EEC Text with EEA relevance. OJ L 70, 16.3.2005, p. 1-16.

less active substance. Co-formulants do not exhibit pesticidal activity but may still be biologically or chemically active and may therefore elicit adverse effects on target and non-target organisms. A list of all co-formulants used in plant protection products in Germany has been published by the German BVL (*personal communication, P. Bormann, BLW*)<sup>3</sup>.

## 2.2 Pesticide residues

Traces of pesticides that are left in food and animal feed products are called '*pesticide residues*'. According to Regulation (EC) No 396/2005 (Art.3, par.2, let.c)<sup>2</sup> '*pesticide residues*' means *residues, including active substances, metabolites and/or breakdown or reaction products of active substances currently or formerly used in plant protection products*'. This is equivalent to the Swiss definition as given in the Regulation on the maximum levels for pesticide residues in or on products of plant and animal origin (VPRH)<sup>1</sup>. Consumers may be exposed to pesticides because residues may remain on harvested crops after treatment. These pesticide residues must be as low as technically possible (ALARA principle, '*as low as reasonably achievable*') based on Good Agricultural Practice (GAP), and must be safe for consumers. The highest amount of pesticide that is legally tolerated to remain in or on a given product is called the '*maximum residue level*' (MRL) (see **section 5.2**). It is not a toxicological limit, and exceedance is not necessarily a cause of concern for public or animal health (see **section 6.1**).

## 2.3 Chemical mixture

### 2.3.1 What is a chemical mixture under EU and Swiss legislation?

The term '*chemical mixtures*' refers to combined exposure (either simultaneously or sequentially) to two or more different chemicals via common or different routes (e.g. oral, dermal, inhalation) of exposure from common or different sources of exposure (e.g. air, food, water, medicines, consumer goods). The term is not specific to mixtures of pesticides but is used in many different contexts where chemicals combine to produce an effect. REACH and CLP Regulations use the term '*mixture*' for a '*mix or solution of two or more substances*'. In Swiss legislation, the term *preparation* is used (De: *Zubereitung*, Fr: *préparation*) in the ChemV<sup>4</sup>, ChemRRV<sup>5</sup>, and PSMV<sup>6</sup> Ordinances.

### 2.3.2 What are the different types of chemical mixtures encountered in the chemical legislation?

From a regulatory perspective, basically four different types of mixtures may be distinguished in the context of EU chemicals legislation<sup>7</sup>, each requiring different strategies for risk management:

- (i) *Chemicals that are legally registered as single substances on the EU market, but which are mixtures in themselves, so-called multi-constituent substances (MCS) and materials of unknown or variable composition, complex reaction products or biological materials (UVCBs)*.

<sup>3</sup> [https://www.bvl.bund.de/SharedDocs/Downloads/04\\_Pflanzenschutzmittel/zul\\_info\\_liste\\_beistoffe.html](https://www.bvl.bund.de/SharedDocs/Downloads/04_Pflanzenschutzmittel/zul_info_liste_beistoffe.html)

<sup>4</sup> SR 813.11. Verordnung über den Schutz vor gefährlichen Stoffen und Zubereitungen (Chemikalienverordnung, ChemV) vom 5. Juni 2015 (Stand am 1. März 2018).

<sup>5</sup> SR 814.81. Verordnung zur Reduktion von Risiken beim Umgang mit bestimmten besonders gefährlichen Stoffen, Zubereitungen und Gegenständen (Chemikalien-Risikoreduktions-Verordnung, ChemRRV) vom 18. Mai 2005 (Stand am 1. März 2018).

<sup>6</sup> SR 916.161. Verordnung über das Inverkehrbringen von Pflanzenschutzmitteln (Pflanzenschutzmittelverordnung, PSMV) vom 12. Mai 2010 (Stand am 1. Januar 2018).

<sup>7</sup> Kortenkamp, Backhaus and Faust, 2009; refined upon personal communication with the authors.

- (ii) *Intentionally prepared mixtures of known composition that are placed on the EU market as chemical products (formerly denoted as preparations<sup>8</sup>).* Marketed plant protection products fall under this category. Plant protection products are complex formulations<sup>9</sup> which contain, besides the active substance responsible for the pesticidal activity, additional chemical ingredients or 'co-formulants' (see section 2.1).
- (iii) *Mixtures of chemicals of known or unknown composition jointly released from a single source, such as a production, transportation, consumption or recycling process; sometimes referred to as 'generated' mixtures.*
- (iv) *Complex mixtures of chemicals co-occurring in environmental media (water, soil, air), biota, feed, food, or human tissues as a result of releases from various sources and through multiple routes of exposure; these are mixtures of unknown/varying composition.*

The focus of this report is primarily on (iv) since pesticide residues are covered here.

## 2.4 Combination effect

Combination effects, also known as '*cocktail effects*', can occur in case of exposure to different chemicals present in a mixture. Three types of cocktail effects can be defined that can change the risk of adverse effects (see section 4.1):

- **Additive effect:** effects from individual chemicals in the mixture summed up.
- **Synergistic effect:** the individual chemicals in the mixture reinforce each other's effect, resulting in combined effects greater than the sum of the individual effects (referred to as '*supra-additive*' or '*greater-than-additive*').
- **Antagonistic effect:** the individual chemicals in the mixture reduce or cancel out each other's effect(s), resulting in combined effects smaller than the sum of the individual effects (referred to as '*less-than-additive*').

## 2.5 Endocrine disruption

Effects of chemical mixtures are often discussed in the context of so-called '*endocrine disruption*'. A chemical with endocrine disrupting properties (also termed '*endocrine disruptor*') can be defined as "*an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations*". (WHO/IPCS, 2002). Several endocrine modes of action have been identified that involve e.g. perturbations on the Estrogenic, Androgenic, Thyroid and Steroidogenesis (EATS) axes.

## 2.6 Low dose effect

The concept of '*low dose effect*' is not specifically related to chemical mixtures, however both concepts are frequently jointly discussed or mixed up in the public and media discourse. The so-called '*low-dose*

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<sup>8</sup> While the term "*preparation*" has been replaced by "*mixture*" in the new Regulation (EC) 1272/2008 on Classification, Labelling and Packaging of substances and mixtures (CLP), in other pieces of EU legislation like the Plant Protection Product Regulation (EC/1107/2009), the term "*preparation*" continues to be used.

<sup>9</sup> 'Preparations', i.e. mixtures or solutions composed of two or more substances intended for use as a plant protection product or as an adjuvant (Regulation EC/1107/2009, Art.3).

*hypothesis'* postulates that low doses of chemicals can have effects that would not necessarily be predicted from their effects at high doses (biphasic response to exposure, hormesis). There is no consensus yet on a definition for low dose effects; different working definitions have been proposed, including (Melnick et al., 2002):

- *Effects that occur in the typical range of human exposures;*
- *Effects that occur at environmentally-relevant doses;*
- *Effects observed at doses below those used in toxicity testing, or at doses below the presumed No-Observed (Adverse) Effect Level or Benchmark Dose<sup>10</sup>.*

The concept of low dose effects is primarily discussed in the context of endocrine disrupting chemicals and remains controversial and the subject of intense research (Vandenberg et al., 2012; Rhomberg and Goodman, 2012).

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<sup>10</sup> 'No-Observed (Adverse) Effect Level' (NO(A)EL and 'Benchmark Dose' (BMD) are terms used in regulatory toxicology studies to describe the highest administered or calculated dose of a substance that does not result in a statistically or biologically significant increase in frequency or severity of an (adverse) effect.

### 3 General background

#### 3.1 Brief historical overview of risk assessment of chemical mixtures: how did it start?

The first theoretical considerations about combinations of chemicals have likely paralleled the developments of the modern chemical industry since the mid XIX<sup>th</sup> century (e.g. crude oil refinery, manufactured fuel gas; Rowe, 1998) as well as progress in pharmacology in the first quarter of the XX<sup>th</sup> century (Loewe et al., 1926; Macht, 1929), but it was really in the 1930s-1950s that the principles of mixture toxicology and the first conceptual frameworks (see also **section 4.1**) were laid down with the pioneering works from Bliss (1939), Finney (1942), and Plackett and Hewlett (1948, 1952)<sup>11</sup>.

It can generally be observed that more recent scientific and regulatory developments in risk assessment of chemical mixtures in the US and EU have been largely driven by legal mandates to address the toxicity of chemical mixtures (see **section 3.3**)<sup>12</sup>.

In the US, groundbreaking activities in the late 1980s by the US Environmental Protection Agency (USEPA, 1986) and other US governmental institutions (NRC, 1994; PCC, 1997) lead to the development of guidelines and methodologies for assessing human health risks from chemical mixtures (USEPA, 2007). In particular, the Food Quality Protection Act (FQPA) for child protection from pesticides requires USEPA to consider cumulative exposure to pesticide residues that have common mechanisms of toxicity (FQPA, 1996). Following the release of its Framework for Cumulative Risk Assessment (USEPA, 2003), the Agency performed Cumulative Risk Assessments for five classes of pesticides (*organophosphates, carbamates, triazines, chloroacetanilides, and pyrethrins/pyrethroids*).

In the EU, explicit legal requirements to address cumulative or synergistic effects of chemicals mixtures were gradually introduced in various pieces of chemical legislation since the early 2000s (see **section 3.2**). Over the last decade, intense research and regulatory efforts have been dedicated to better characterizing the toxicity of mixtures and develop novel procedures and methodologies for assessing hazards and risks of chemical mixtures, in particular in the field of pesticides and food safety (EFSA, 2008, 2012, 2013a; Kortenkamp et al., 2009; EC, 2012a, ECETOC, 2012) (see **section 6.3.1**).

At international level, the International Programme on Chemical Safety of the World Health Organisation (WHO/IPCS) has issued recommendations for best practice in terminology issues and harmonisation (WHO/IPCS, 2009), and has developed a framework for the risk assessment of combined exposure to multiple chemicals (Meek et al., 2011). Building on the WHO/IPCS framework, the Organization for Economic Cooperation and Development (OECD) is currently developing a guidance on combined exposures to multiple chemicals<sup>13</sup>.

<sup>11</sup> A discussion of these pioneer activities can be found in Plackett and Hewlett (1952), and Könemann and Pieters (1996).

<sup>12</sup> Kienzler et al. (2016) have recently reviewed the current safety requirements for intentional and coincidental chemical mixtures of unknown/varying composition in several regulatory frameworks at regional (EU, US, Canada) and international (WHO, OECD) level, as well as existing guidance documents on mixture toxicity assessment in these jurisdictions (JRC, 2014).

<sup>13</sup> The OECD Guidance aims at improved technical convergence/harmonisation of existing approaches and methodologies, with a link to various other ongoing projects, in particular on Adverse Outcome Pathways (AOPs), <http://www.oecd.org/chemicalsafety/risk-assessment/oecdactivitiesonexposureassessment.htm#CombinedEX>

### 3.2 Are combination effects of pesticide mixtures addressed by legislation and risk assessment?

#### 3.2.1 What are the legal requirements for taking pesticide mixtures toxicity into account?

Health risks from pesticide mixtures are covered by different pieces of EU and Swiss chemical legislation regulating the marketing of pesticides and setting of maximum residue limits (MRLs) in food, a central and guiding requirement being that pesticides and their residues should have no harmful effects - including cumulative and synergistic effects - on humans. Explicit legal requirements to address health risks of pesticide mixtures have been introduced in several EU sectorial chemical regulations (MRL, PPP, and BP Regulations). The EU legal provisions have been largely transposed in the corresponding Swiss chemical legislation, pending a few adaptations and minor modifications.

- Regulation (EC) 396/2005 on maximum residue levels (MRLs) of pesticides in food stipulates that decisions on MRLs should take into account cumulative and synergistic effects of pesticides when the methods to assess such effects become available (*recital 6; Art. 14, par. 2, let. b; Art. 36, par. 1, let. c*; see **Appendix II**). The Swiss Ordinance on pesticide residues (VPRH)<sup>14</sup> largely repeats the provisions of Regulation (EC) 396/2005, but with some modifications and adaptations to the Swiss legislation context<sup>15</sup>, in particular regarding pesticide residues evaluation and the setting of MRLs in Art. 14 and Art. 16 of Regulation (EC) 396/2005. With respect to combined effects of pesticides (Art. 14, par. 2, let. b) where the European legislation stipulates that the assessment must take place only once methods are available for assessing cumulative and synergistic effects, the Swiss ordinance requires taking into account the known cumulative and synergistic effects of the active substances which affect the same biological system (VPRH, Art. 3, par. 2, let. i; see **Appendix III**) (BLV, 2017a).
- The Plant Protection Products Regulation (EC) 1107/2009 covering the placing of pesticides on the market stipulates that pesticides and their residues, with regard to realistic conditions of use and potential sources of direct or indirect exposure, shall have no immediate or delayed harmful effects on human or animal health, "*taking into account known synergistic and cumulative effects where the scientific methods accepted by the Authority to assess such effects are available*" (Art. 4, par. 2, let. a; Art. 4, par. 3, let. b; see **Appendix II**). The same wording is used in the Swiss Ordinance on Plant Protection Products<sup>16</sup> (PMSP, Art. 4, par. 3, let. a; Art. 4, par. 5, let. b; see **Appendix III**). Regulation (EC) No. 1107/2009 also requires that "*interaction between the active substance, safeners, synergists and co-formulants shall be taken into account*" in the evaluation and authorisation of plant protection products (Art. 29).
- The PMSP also references the Regulation EU 284/2013 setting out the data requirements for plant protection products (EC, 2013), which stipulates that "*any information on potentially harmful effects of the plant protection product on human and animal health or on groundwater shall be included as well as known and expected cumulative and synergistic effect*". Applicants are therefore required to submit data to allow for an assessment of acute and chronic consumer exposure, including, where relevant, a cumulative risk assessment deriving from exposure to more than one active substance. Similarly, the exposure assessment of operators, workers, residents and bystanders shall also be

<sup>14</sup> SR 817.021.23. Verordnung des EDI über die Höchstgehalte für Pestizidrückstände in oder auf Erzeugnissen pflanzlicher und tierischer Herkunft (Verordnung über Pestizidrückstände, VPRH) vom 16. Dezember 2016 (Stand am 1. Mai 2018).

<sup>15</sup> Unlike the EU, Swiss food legislation does not regulate feed. As a result, the feed provisions, including the animal health RA, have not been included in the VPRH. Biocides and some other contaminants are integrated in the VPRH, the tolerances values are abandoned to keep only the maximum residue limit values (BLV, 2017a).

<sup>16</sup> SR 916.161. Verordnung über das Inverkehrbringen von Pflanzenschutzmitteln (Pflanzenschutzmittelverordnung, PMSP) vom 12. Mai 2010 (Stand am 1. Januar 2018).

conducted including, where relevant, the cumulative exposure to more than one active substance (see Annex, Introduction section). Cumulative and synergistic effects shall be taken into account and reported in the dossier in cases where the product label includes requirements for use of the plant protection product with other plant protection products (PPPs) or with adjuvants as a tank mix, and the exposure assessment shall cover the combined exposure. Bystander and resident exposure information shall be provided to permit an assessment of the extent of exposure to the active substances and toxicologically relevant compounds likely to occur under the proposed conditions of use, taking into account, where relevant, cumulative and synergistic effects. It shall also provide a basis for the selection of appropriate protective measures, including restricted entry intervals, exclusion of residents and bystanders from treatment areas and separation distances. An estimation shall be made, using where available a suitable calculation model in order to permit an evaluation of the bystander and resident exposure likely to arise under the proposed conditions of use. Where relevant, this estimation shall take into account cumulative and synergistic effects resulting from the exposure to more than one active substance and toxicologically relevant compounds, including those in the product and tank mix.

- The Biocidal Products Regulation (EU) 528/2012 covering the placing of biocidal products on the market stipulates that, in order to ensure a high and harmonised level of protection of human health, animal health and the environment, an "*assessment of the risks associated with the relevant individual components of the biocidal product [shall be carried out], taking into account any cumulative and synergistic effects*". It is further specified that all relevant stakeholders shall "*develop and provide further guidance on the scientific definitions and methodologies for the assessment of cumulative and synergistic effects*" (Annex VI, par. 3, par. 15, par. 53; see **Appendix II**). The Swiss Ordinance on Biocide Products<sup>17</sup> specifies that cumulative and synergistic effects have to be taken into account when setting maximum levels for biocides (VBP, Art. 11b, let. d and e; see **Appendix III**). The VPRH covers also residues from biocides (VPRH, Art. 3, par. 2, let. d; see **Appendix III**).

### **3.2.2 Are health risks from chemical mixtures addressed by regulatory risk assessment?**

Generally speaking, in contrast to single substance assessments, mixture risk assessment for human (or environmental) safety is a developing and not yet a well-established standard procedure in EU regulatory processes. There is currently no mechanism for a systematic, comprehensive and integrated assessment of mixture effects taking into account different routes of exposure and different product types (EC, 2012b). Therefore, while the different sectorial chemical legislations set strict limits for the amounts of particular chemicals allowed in food, water, air and manufactured products, the potential risks resulting from the combined effects of these chemicals are in practice rarely taken into consideration (Kienzler et al., 2016). There are a few examples of chemical mixtures assessments and controls being carried out under EU legislation in relation to several substances originating from different sources and through different pathways, including mixtures released from a single source (e.g. factory, facility), but these are limited in their scope (EC, 2012b). Typically, chemical mixtures that are regulated and assessed for safety relate to products of known composition such as plant protection formulations (see **section 2.3**). These considerations apply equally to the Swiss regulatory landscape for chemicals including pesticides.

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<sup>17</sup> SR 813.12. Verordnung über das Inverkehrbringen von und den Umgang mit Biozidprodukten (Biozidprodukteverordnung, VBP) vom 18. Mai 2005 (Stand am 1. März 2018).

### 3.3 How are plant protection products regulated in Switzerland?

Before they can be placed on the market and used, plant protection products (PPPs) are subject to an extensive and stringent authorization procedure to ensure that active substances and products are safe for human and animal health, including their residues in food and feed, and for the environment. The application dossier contains the legally required (eco)toxicity studies which are carried out under the responsibility of the applicants. In Switzerland, the Federal Office for Agriculture (FOAG) is the lead competent authority with regard to authorization or prohibition of PPPs. The regulatory landscape for plant protection products in Switzerland involves several Federal Authorities and research institutes. It splits competences in risk assessment and risk management (see **Figure 1**). The legal basis is the Ordinance on chemicals (ChemV)<sup>18</sup>, the Ordinance on plant protection products (PSMV)<sup>16</sup>, and the Ordinance on pesticide residues (VPRH)<sup>14</sup>. Switzerland is in line with the corresponding EU legislation, pending some differences and minor adaptations (see **section 3.2.1**). PPPs can be marketed only after approval by the FOAG. In principle, each application for approval is examined by four assessment bodies that are responsible for the scientific evaluation of (eco)toxicity studies to assess potential health and environmental risks from the use of PPPs<sup>19</sup>:

- The **Federal Office for Food Safety and Veterinary Affairs (FSVO)** is concerned with consumer safety, classification and labelling, and the setting of MRLs of pesticides in food, but also with the exposure assessment and safety of residents in a non-occupational setting when exposed to PPPs when gardening or to a drift during spraying<sup>20</sup> (bystanders);
- The **Federal Office for the Environment (FOEN)**, is concerned with the environmental impact of PPPs (soil, water, air) and the application of the legislation in the environmental context<sup>21</sup>;
- The **State Secretariat for Economic Affairs (SECO)** is concerned with occupational safety of professional users during direct application of PPPs or during post-treatment work<sup>22</sup>;
- The **Agroscope stations** are involved both with assessment activities as well as providing scientific support to the FOAG in areas related to chemical specification and PPP identity, use patterns and efficacy; evaluation of PPP residues in crops; groundwater quality; environmental toxicity, fate and impact; and risk management of PPPs<sup>23</sup>.

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<sup>18</sup> SR 813.11. Verordnung über den Schutz vor gefährlichen Stoffen und Zubereitungen (Chemikalienverordnung, ChemV) vom 5. Juni 2015 (Stand am 1. März 2018).

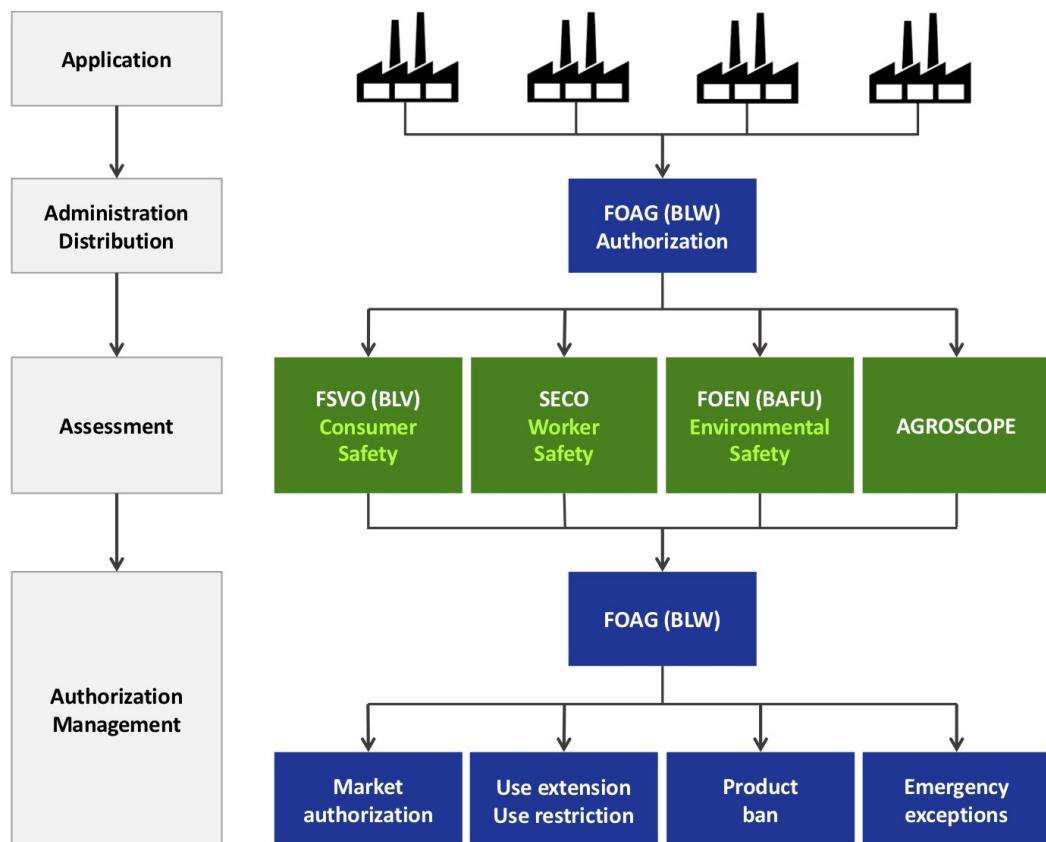
<sup>19</sup> <https://www.blw.admin.ch/blw/de/home/nachhaltige-produktion/pflanzenschutz/pflanzenschutzmittel.html>

<sup>20</sup> <https://www.blv.admin.ch/blv/fr/home/lebensmittel-und-ernaehrung/lebensmittelsicherheit/stoffe-im-fokus/glyphosat.html>

<sup>21</sup> <https://www.bafu.admin.ch/bafu/de/home/themen/chemikalien/dossiers/pflanzenschutzmittel.html>

<sup>22</sup> <https://www.seco.admin.ch/seco/fr/home/Arbeit/Arbeitsbedingungen/Chemikalien-und-Arbeit/Pflanzenschutzmittel.html>

<sup>23</sup> <https://www.agroscope.admin.ch/agroscope/de/home/themen/pflanzenbau/pflanzenschutz/pflanzenschutzmittel.html>

**Figure 1: Authorization procedure for plant protection products in Switzerland**

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### 3.4 Why is mixture toxicity challenging the current regulatory risk assessment paradigm for chemicals (including pesticides)?

In real-life exposure conditions, humans and animals are simultaneously exposed to multiple chemicals from multiple exposure sources. However, current health risk assessment approaches for evaluating the safety of chemicals are usually carried out on one substance at a time, considering only a single source of exposure. The number of chemicals to which humans potentially are concurrently exposed is enormous. Efficient testing strategies and assessment methodologies for evaluating the hazards and risks of chemical mixtures are still largely lacking. Therefore, concerns have been expressed about the current limitations of assessing compounds individually, and the need to adequately understand and assess risks associated with chemical mixtures (EC, 2012b). Yet understanding how chemical mixtures behave is complex, because the number of combinations of chemicals is almost infinite, ever changing in concentrations, and the exact mixture composition largely unknown (Kienzler et al., 2016). Knowledge is still largely lacking on where, how often and to what extent humans are exposed to certain chemical mixtures and how exposure may change over time. Interactions of chemicals in mixtures are difficult to foresee, particularly for long-term effects (EC, 2012b). A pesticide active ingredient present in a mixture can have different properties and different toxicological effects at different doses and at different sites. Testing every possible combination of chemicals is neither realistic nor useful. New tools, methods and risk-based approaches are therefore needed.

While the sectorial chemical legislations set strict limits for the amounts of particular chemicals allowed in food, water, air and manufactured products, the potential risks resulting from the combined effects of these chemicals are in practice rarely taken into consideration (Kienzler et al., 2016). There is currently no systematic mechanism for assessing mixture toxicity in the wide body of EU chemical legislation. Explicit legal

requirements for taking mixture toxicity into account are confined to some specific types of mixtures and to some very specific parts of the chemical legislation (see **section 2.3** and **section 3.3**). This situation raises concerns about different levels of safety assessment requirements under different regulations, calling for an improvement of consistency across the different pieces of EU chemicals legislation<sup>24</sup>. Addressing these science and regulation issues is complex, but the development of the corresponding procedures and methodologies is currently under way (see **section 6.3**).

### **3.5 Is there a need for scientific and regulatory action?**

Concerns have been expressed about the current limitations of assessing compounds individually, and the need to adequately understand and assess potential health risks for the general population from chemical mixtures has been identified (see **section 3.4**). Various scientific and regulatory gaps and needs in the area of chemical mixture assessment have been recognized in recent years (e.g. EFSA, 2008; Kortenkamp et al., 2009; EC, 2012a, 2012b; Kienzler et al., 2016): (i) the need to generate new hazard data, in particular on the mode of action of chemical mixtures to support grouping in cumulative assessment groups (CAGs); (ii) the need to identify the drivers of mixture toxicity under realistic exposure scenarios; (iii) the need for monitoring or modelling exposure data under realistic exposure scenarios; (iv) the need for new toxicity testing strategies, predictive tools and risk assessment methodologies; (v) the need for more harmonised terminology, consistent procedures and safety requirements across the different sectorial chemical regulations. Action has already been taken, both at the science and policy levels, through national and international, multi-sector, multi-stakeholder research and regulatory initiatives and programmes (e.g. WHO/IPCS, 2009a; EC, 2012a; OECD, 2011; ECETOC, 2012; EFSA, 2007). The corresponding procedures, tools and methodologies are currently under development; in particular, the area of mixtures of pesticide residues in food and drinking water benefits from intense research and regulatory activity (EFSA, 2016, 2018a)<sup>25,26,27,28</sup> (see **section 6.3**). Specific provisions regarding combined effects of chemical including pesticide mixtures already exist in the chemical and food legislation (see **section 3.2**).

In parallel, additional measures and complementary approaches have to be sought. Strategies for achieving sustainable use of pesticides and minimizing their overall impact on human health and the environment, such as promoting the use of integrated pest management, have already been implemented at EU and Swiss level<sup>29,30,31</sup>, incl. through regulation<sup>32</sup>. Similar to the EU strategy, Switzerland has implemented a National Action Plan for risk reduction and sustainable use of PPPs, which defines 8 main objectives and 12 concrete intermediate objectives, with over 50 accompanying measures in three areas (application, specific risks and accompanying instruments). These measures are constantly being expanded and adapted to needs. Although they are not specifically focused on pesticide mixtures, they contribute to reducing the amount and potential health impact of traces of multiple pesticide residues in food and drinking water.

<sup>24</sup> Kortenkamp, Backhaus and Faust, 2009; refined upon personal communication with the authors.

<sup>25</sup> <https://www.efsa.europa.eu/en/press/news/160127>

<sup>26</sup> <https://www.efsa.europa.eu/en/press/news/180419>

<sup>27</sup> EFSA has just closed a public consultation on a draft scientific report on the establishment of cumulative assessment groups of pesticides for their effects on the nervous system, <https://www.efsa.europa.eu/en/consultations/call/180508-0>

<sup>28</sup> [https://www.rivm.nl/en/Topics/F/Food\\_safety/EFSA\\_RIVM\\_Partnership](https://www.rivm.nl/en/Topics/F/Food_safety/EFSA_RIVM_Partnership)

<sup>29</sup> [https://ec.europa.eu/food/plant/pesticides/sustainable\\_use\\_pesticides\\_en](https://ec.europa.eu/food/plant/pesticides/sustainable_use_pesticides_en)

<sup>30</sup> Postulat Moser 12.3299 von 16 März 2012, Aktionsplan zur Risikominimierung und nachhaltigen Anwendung von Pflanzenschutzmitteln, <https://www.parlament.ch/de/ratsbetrieb/suche-curia-vista/geschaef?AffairId=20123299>

<sup>31</sup> <https://www.blw.admin.ch/blw/de/home/nachhaltige-produktion/pflanzenschutz/aktionsplan.html>

<sup>32</sup> Directive 2009/128/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for Community action to achieve the sustainable use of pesticides (Text with EEA relevance).

## 4 Hazard of pesticide mixtures

### 4.1 What is currently known about the combined effects of pesticide mixtures?

#### 4.1.1 What are the general principles of mixture toxicology?

The scientific basis for mixture effects through similar action, independent action, and synergistic or antagonistic action was laid down in the 1920s-1950s (see **section 3.1**). Synergistic and antagonistic effects of different mixtures of phenacetin, acetylsalicylic acid and codeine were described by Loewe et al. (1926). Bliss (1939) described synergistic effects of mixtures of two insecticides, pyrethrin and rotenone, and combined effects through dissimilar action of mixtures of nitro-phenol and petroleum oil. Work by Finney (1942) and Plackett and Hewlett (1948, 1952) further contributed to extend the work from Bliss and develop the first conceptual frameworks for combined (toxic) effects of chemical and pesticide mixtures (as outlined by Könemann and Pieters, 1996).

The principles of mixture toxicology are now well established (Kortenkamp et al., 2009; Boobis et al., 2011; EC, 2012a; ECETOC, 2012). Under certain conditions, chemicals in a mixture will act jointly in such a way that the overall level of toxicity is affected, which may change the risk of adverse effects. Chemicals can have combined effects through a similar or dissimilar mode of action (MoA)<sup>33</sup> in a non-interactive manner, or in an interactive manner through synergy and antagonism. Three major types of combined effects can be defined: (i) **additive effects**; (ii) **synergistic effects**; and (iii) **antagonistic effects** (see **Table 2**).

Individual chemicals in the mixture may work via a common or sufficiently similar MoA to produce combined effects that are larger than the effects of each mixture component taken in isolation. The dose of each individual chemical corrected for potency can simply be added to predict the magnitude of the effects. This concept can be described as '**dose addition**' (the toxic outcome being the same). In other cases, each chemical in the mixture may act via an independent, dissimilar MoA, but eliciting broadly the same toxicological effects; these effects would then have to be taken into account individually in a weight of evidence approach. This is referred to as '**response addition**', assuming the addition of the response. Not all mixture components contribute equally to the toxic effects; the toxicity of real-life mixtures is typically driven by 1-2 chemical(s) in the mixture (ECETOC, 2012).

If the individual chemicals in the mixture combine to become more toxic ('synergy') or less toxic ('antagonism'), this is referred to as '**interaction**'<sup>34</sup>. In the case of **synergy**, individual chemicals in the mixture combine in such a way they reinforce each other's effect and become more toxic, whereas in the case of **antagonism**, they reduce or cancel out each other's effect(s) and become less toxic. Exposure to such mixtures would result in combined effects that are greater or smaller than the sum of the individual effects of the mixture's component, respectively. Additivity and independent action probably account for the majority of toxic effects of chemical mixtures. Dose addition for similarly acting chemicals and response addition for dissimilarly acting chemicals have therefore been proposed as default assumptions for risk assessment. Synergistic effects are usually observed experimentally at high doses and are considered to occur only rarely at environmentally relevant exposure concentrations such as in the dietary context (see **section 4.1.2**).

<sup>33</sup> The concept of mode of action (MoA) describes the sequence of key biological events leading from initial exposure to a chemical to an adverse effect at the cellular, organ and/or individual level.

<sup>34</sup> The way pesticide mixtures may interact with biological and physiological processes depend on factors such as relative doses and potency of each component; exposure pathways, routes, frequency and duration; and the biological targets. Interaction might occur at toxicokinetic level (changes in absorption, distribution, metabolism, and/or elimination processes) or at toxicodynamic level (involving different target sites for the same molecular and cellular processes) (Hernández et al., 2017).

Even for pesticides, which are extensively investigated in comparison with other chemicals, detailed knowledge on the MoA is the exception rather than the rule. MoAs have been established only for a very few groups of pesticides (ca. 10%) and notably not even for all the effects they induce. This has implications for mixture risk assessment. Consideration of MoA information typically involves one type of effect for grouping pesticides according to their specific potencies, but it should be born in mind that pesticides also exert effects other than the one used for grouping.

**Table 2: Overview of the different types of combined effects**

Type of combined effect	Subtypes	Synonyms	Effects observed
Non-interactive	Simple similar action	Additivity	Dose addition
	Simple dissimilar action	Independent action	Response addition
Interactive	Synergy		> Dose additivity
	Antagonism		< Dose additive effects

(Source: modified from ECETOC, 2012)

#### 4.1.2 What is the evidence for combined effects of chemical mixtures and pesticides residues?

Moretto (2008) reviewed combined effects of chemical and pesticide mixtures and observed that: (i) mixture components with the same MoA show dose-additivity at low doses and at high doses (although all possible types of combined effects may occur at high doses); (ii) mixture components with dissimilar MoAs do not show dose-additivity at doses below the no-observed adverse effect level (NOAEL) of each individual component; (iii) mixtures of components with dissimilar MoAs show all the effects of the individual components at higher doses. This was generally confirmed by later assessments (e.g. EC, 2011; ECETOC, 2012a; JRC, 2014) and reviews (e.g. Boobis et al., 2011; Kienzler et al., 2016; Rizzati et al., 2016; Hernández et al., 2017). The available body of evidence suggests that dose-addition and interactions (such as synergy and antagonism, see **Table 2**) could possibly occur under certain conditions, but response-addition will occur rarely in practice.

Most studies on pesticide mixture toxicity have been conducted in *in vitro* and *in vivo* models using high experimental exposure concentrations at effect levels (e.g. studies with endocrine endpoints such as Medjakovic et al., 2014 and Ghisari et al., 2015). Studies using low doses at or below the NOAEL are comparatively rare (Moretto, 2008; Boobis et al., 2011; ECETOC, 2012). For mixture studies conducted at or close to the NOAELs of the components, toxicity (e.g. neurotoxicity, nephrotoxicity, hepatotoxicity) is expected based on dose-additivity, because summation of effects which are not detectable for single compounds at the NOAEL can occur (ECETOC, 2012). It is noteworthy that not all pesticides have an acute reference dose, and very often short-term and chronic studies have similar NOAELs (Zarn and O'Brien, 2018). This implies that there might be a need to consider also temporally slightly shifted short-term exposures as combined exposures. Where there are concerns over specific mixtures, they must be studied on a case by case basis taking all available information (i.e. on MoA, hazard, exposure) into account. For practical reasons, additivity remains the most common default assumption used in mixture risk assessment, and dose addition is generally seen as a conservative initial step.

A very large synergistic interaction would have the potential to compromise a risk assessment even when each chemical is well below maximum acceptable exposure level (ECETOC, 2012). In general, chemical interactions (as defined in **Table 2**) have been found to be sufficiently uncommon and small (Boobis et al.,

2011; ECETOC, 2012; Hernández et al., 2017)<sup>35</sup>; in particular, synergy appears to be dose-dependent and to occur primarily at high doses, but toxic effects are possible in some circumstances at doses below the NOAEL of each individual mixture component. Boobis et al. (2011) found that the magnitude of synergy at low doses did not exceed the levels predicted by additive models by more than a factor of 4 (Hernández et al., 2017). Little significant evidence has been found so far of synergistic effects at low doses of mixtures of chemicals with endocrine toxicity (Kortenkamp et al., 2009; Boobis et al., 2011; Gaudriault et al., 2017). It is generally considered that interactive effects such as synergy from multiple pesticide residues are less likely to occur at doses relevant to the human dietary exposure context (Moretto, 2008; Boobis et al., 2011; ECETOC, 2012; Hernandez et al., 2016; Rizzati et al., 2017)<sup>36</sup>. While relatively low levels of exposure to pesticide residues in food are expected for the general population (see **section 5.2** and **section 5.3**), this may be different in an occupational context (i.e. industrial or agricultural setting) where workers and farmers could be potentially exposed to much higher concentrations of pesticide mixtures during activities such as manufacture, transport, storage, application, and disposal.

## 4.2 Are pesticide mixtures assessed for safety?

### Intended mixtures (type ii, see **section 2.3.2**)

When authorizing a plant protection product (PPP), toxicological data on the active substance and the co-formulants are required under the EU PPP and Swiss PSMV Regulations, and under the EU REACH and Swiss ChemV Regulations (depending on the tonnage), respectively. Hazard and risk assessments of PPPs should ideally be based on toxicity tests with the final formulated product ('whole mixture approach', see **section 4.3**). However, such mixture testing and assessment is confined to the acute human toxicity following direct contact with the product. Therefore, for practicability reasons and costs, studies on the final product are only required for selected acute toxicological endpoints, e.g. dermal absorption when justified<sup>37</sup> (EU/284/2013, Annex, Part A, Section 7.3). Chronic studies are not carried out with formulations, but the toxicity data of the individual co-formulants (see **section 2.1**), e.g. data for registered chemicals in the REACH database, are used to assess the toxicity of a formulated product. In practice, however, data are often scarce, but if available, they are taken into account in the evaluation process. Using the international Globally Harmonized System (GHS), the total toxicity of the formulated product is then determined on the basis of the individual substance data. The assessment of coincidental mixtures of pesticides (i.e. mixtures unintentionally formed during the production process, or mixtures released in the environment; see **section 2.3**) is generally not required (Kienzler et al., 2016).

Co-formulants may also contribute to the overall toxicity of a mixture on target or non-target organisms as shown for *tallowamine* in *glyphosate*-based formulations (Defarge et al., 2016). The Swiss Federal Office for

<sup>35</sup> The evidence for pesticides interactions is still very limited and has been documented experimentally for *potentiating effects* (malathion by isomalathion, pyrethroid, carbaryl and triazine herbicides by organophosphates; organophosphates by organochlorines), *synergistic effects* (pyrethroids and carbamates; organochlorines and carbamates; triazole and dicarboximide fungicides; organophosphate, pyrethroids, triazoles, and triazine), or *antagonistic effects* (triazine herbicides and prochloraz) (Hernández et al., 2013, 2017). Rizzati et al. (2016) reported that additive effects were frequently observed except with herbicide mixtures; synergism was mainly reported for insecticide mixtures, and antagonism was fairly uncommon. Neurotoxicity was mainly associated with insecticide mixtures, and most studies with fungicide mixtures were associated with effects on endocrine regulation and/or reproduction.

<sup>36</sup> While some argue that the concentrations of individual pesticides are too low for any significant interactions to occur in the dietary context (Moretto, 2008; Boobis et al., 2011; ECETOC, 2012; Hernandez et al., 2016; Rizzati et al., 2017), it has also be pointed out that this assumption should be carefully considered in the context of statistically low powered toxicity studies (Zarn and O'Brien, 2018).

<sup>37</sup> "Die Untersuchung ist durchzuführen, wenn die Hautexposition einen Hauptexpositionsweg darstellt und die Risikoabschätzung auf Basis des Standardabsorptionswerts kein annehmbares Risiko ergibt" (EU/284/2013, Annex, Part A, Section 7.3, *Notwendigkeit der Abschätzung*).

Agriculture (FOAG) is working with the other chemicals offices to develop a strategy to ensure that all available toxicological data on co-formulants are centrally recorded and thus available for assessment (*personal communication, P. Bormann, FOAG*). Critical co-formulants are included in a negative list as mentioned above and may then no longer be permitted in plant protection products. In order to prevent harmful substances from being used in PPPs, a so-called negative list of co-formulants that may not be used or no longer used in PPPs is planned for the future. Annex 3 of the PSMV currently lists as first (and only) substance *tallowamine* with the restriction that the ban applies only for *glyphosate*-based formulations. This goes a step further than the Annex 3 of the PPP Regulation (EC) 1107/2009 which is empty, since in principle it is supposed to list all co-formulants which are not allowed in PPPs. A potential candidate list of co-formulants used in PPPs for Annex 3 has been published by Germany<sup>38</sup>, and a working group has been established by the EU to define a list of co-formulants to be banned (*personal communication, P. Bormann, FOAG; U. Zürcher, FSVO*).

#### Coincidental mixtures (type iv, see section 2.3.2)

The PPP Regulation (EC) 1107/2009 introduced a clear requirement for the consideration of potential mixture effects of PPPs and their residues on human health. However, under Regulation (EC) 396/2005, established procedures for safety assessments of maximum residue levels (MRLs) on the basis of acceptable daily intake (ADI) and acute reference dose (ARfD) values (see section 5.2) and food consumption patterns are *per se* focused on single substance assessments. In this case, the '*whole mixture testing*' approach is not applicable for the assessment of environmental exposure scenarios, where the ingredients of a PPP may be present in different dose ratios compared to the original product. Therefore, component-based modeling approaches have been proposed as a way forward to implement the legal provisions (see section 4.3).

## 4.3 What are the methods, models and tools to test the combined effects of chemical mixtures?

### 4.3.1 What is the general methodology used for chemical mixtures hazard assessment?

The toxicity of chemical mixtures can be assessed by two approaches (EFSA, 2013a; JRC, 2014; Kienzler et al., 2016), i.e. (i) **whole mixture approach** and (ii) **component-based approach**:

- I. Testing the mixture itself (or a mixture with similar composition) as a whole (referred to as '*whole-mixture testing*', also called '*top-down approach*'), using an *in vitro* or an *in vivo* test system. Whole-mixture testing allows to identify unknown components and potential for interactions, but it gives no information on which component is responsible for the interactions or for driving the toxicity of the mixture. The whole mixture approach is used when toxicological data are available either for the mixture itself or for a sufficiently similar mixture which can then be used as a surrogate for the mixture under evaluation.
- II. Testing the individual mixture components (referred to as '*components-interaction analysis*', also called '*bottom-up approach*'). Component-based approaches are preferred methods when dose response data for specific toxicity endpoints of individual components are known so that substances can be placed in cumulative assessment groups (CAGs). This requires data on identity, dose and toxicity, including mode of action (MoA) of the individual compounds. Toxicity and dose information are then integrated for each mixture component to predict the combined effect of the mixture. There are two main applications of this approach: (i) grouping chemicals based on a similar or identical MoA, or (ii) grouping chemicals based on similar toxicity endpoints and common effects, even if the MoAs are unknown. Several models are

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<sup>38</sup> [https://www.bvl.bund.de/EN/04\\_PlantProtectionProducts/01\\_ppp\\_tasks/08\\_ProductChemistry/01\\_ppp\\_coformulants\\_for\\_mulationChemistry/03\\_ppp undesired\\_formulants/ppp undesired\\_formulants\\_node.html](https://www.bvl.bund.de/EN/04_PlantProtectionProducts/01_ppp_tasks/08_ProductChemistry/01_ppp_coformulants_for_mulationChemistry/03_ppp undesired_formulants/ppp undesired_formulants_node.html)

commonly applied to estimate the combined toxicological effect of known chemicals, based on the knowledge of MoA: *dose addition*, *response addition*, and *interaction* (see **section 4.1** and **section 4.3.2**). These approaches have been and are being used worldwide by all major health organizations for regulatory risk assessment of chemical mixtures (reviewed by EFSA, 2013a; JRC, 2014).

In the context of the safety assessment of plant protection products (PPPs), the German Federal Ministry of Food and Agriculture (BMEL), the German Federal Institute for Risk Assessment (BfR) and the European Commission co-organized a workshop in November 2017 on the harmonisation and further development of the human health risk assessment of PPPs (BfR, 2018). Strategies and recommendations for a state-of-the art approach to the toxicological assessment of mixtures were discussed, namely: (i) use of tiered weight of evidence approach to gather all existing data available on the mixture itself (tier 1) and on acute endpoints (acute toxicity, irritation and sensitization; tier 2); (ii) add wherever possible information on similar mixtures to the information from substances included in the mixture in order to use the whole data available; (iii) integrate the available information on single components and similar mixtures or the whole mixture; (iv) use intelligent testing strategies to maximize the use of all existing data prior to any new data generation.

#### **4.3.2 What are the methods and models for testing the toxicity of chemical mixtures?**

There are three types of models to evaluate the combined effects of chemicals with known toxicity (reviewed extensively by JRC, 2014; EC, 2012a; EFSA, 2013a):

- The '**response addition**' (or '**independent action**')-based model assumes that mixture components act independently via a dissimilar mode of action (MoA). This model assumes a combined effect to be the result of statistically independent events<sup>39</sup>; no unacceptable risk to human health is anticipated as long as individual exposure concentrations do not exceed their NOAEL levels.
- The '**dose addition**'-based model assumes that mixture components act additively via the same MoA; here the total response corresponds to the sum of all the individual concentrations multiplied with their respective potencies<sup>40</sup>. This model is based on pharmacological concepts<sup>41</sup> and assumes response additivity if the mixture components share the same biological target. Methods for dose addition approaches most frequently used in human health are the Hazard index (HI)<sup>42</sup>, with variants such as the reference point index (RfPI)<sup>43</sup>, or the Toxic Equivalency Factor (TEF)<sup>44</sup>.

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<sup>39</sup> Response addition refers to the sum of probabilistic risks or incidence, whereas effects addition means the sum of biological responses (Kortenkamp et al., 2009).

<sup>40</sup> Doses of the individual components are added after normalization in relation to an index substance, to account for differences in potency (see TEF, footnote #45 below).

<sup>41</sup> i.e. ligand binding site, affinity, potency, and receptor occupancy. Since receptor occupancy is proportional to ligand concentration and receptor affinity, the magnitude of the biological response to the chemical mixture can be predicted by summing the components doses after adjusting for the differences in potencies.

<sup>42</sup> The HI is the sum of the hazard quotients (HQ), i.e. the ratio between exposure and the reference value for the common toxic effect of each component in a mixture or a CAG (JRC, 2014). Methods for deriving risk estimates for interactions include interaction-based Hazard Index and Hazard Index modified for binary interactions. A typical example of the use of a PBTK includes the derivation of interaction-based Hazard Index using tissue doses accounting for multiple toxicokinetic interactions between the multiple chemicals (EFSA, 2013a).

<sup>43</sup> The RfPI represents the sum of exposures to each chemical component expressed as a fraction of their respective reference points (or points of departure) for the relevant effect (e.g. BMD<sub>10</sub>, NOAEL), in relation to their relative potencies (EC, 2012a).

<sup>44</sup> In this method, the total toxicity of the mixture is assessed in terms of the toxicity of an equivalent concentration of an index compound chosen as reference. The concentrations of mixture components are scaled relatively to the concentration of the index compound, and then summed up. The scaling factor is the TEF. The total equivalent quantity (TEQ) is then estimated by summation of the mixture components doses multiplied by the respective TEF (Kortenkamp et al., 2009).

- The '**interaction'-based model**' assumes that mixture components can reinforce ('synergism') or cancel out ('antagonism') each other's effects. Interactions may occur both at toxicokinetic (TK) or toxicodynamic (TD) level. While this has been demonstrated experimentally for numerous chemicals and contaminants including pesticides at high dose, the relevance of these interactions under realistic low concentrations is a matter of debate.

Additivity is the most common assumption and supposes that combined toxicity of multiple chemicals is additive through either *dose addition* with a similar MoA or *response addition* with a dissimilar MoA; therefore, both concepts have been suggested as default approaches in regulatory risk assessment of chemical mixtures to predict their overall toxicity (EC, 2012a; ECETOC, 2012). Other methods and models include (*inter alia*):

- Full probabilistic models in higher tier risk assessment for exposure assessment (i.e. physiologically-based (PB)-TK models) and for hazard assessment (i.e. Physiologically-based toxicokinetic and toxicodynamic (PBTK/TD) models) (EFSA, 2013a).
- Methods such as read-across for unidentified or partially identified components (e.g. complex mixtures) (here the hazard evaluation is based on toxicity data for a sufficiently similar mixture) or such as the Threshold of Toxicological Concern (TTC)<sup>45</sup> approach for identified components with unknown toxicity (an estimate of exposure for the actual mixture is required here).
- Additional non-predictive tools such as the Maximum Cumulative Ratio (MCR)<sup>46</sup> which can be used to support the risk assessment process by informing on whether a cumulative assessment is needed over a single substance assessment or not, allowing further refinement and characterization of the mixture composition by facilitating the identification of individual or main contributors to the mixture overall toxicity (Kienzler et al., 2016).
- Besides hazard-based models, exposure-based models have been also developed, e.g. in the context of dietary exposure assessment (see **section 4.3.3**).

The routine application of these methods will be facilitated as more data are available (JRC, 2014). Developing criteria for identifying chemical mixtures of priority for risk assessment is essential (see **section 6.3**).

#### **4.3.3 What are the methods available for mixture risk assessment of pesticide residues?**

Intense efforts have been invested over the last decade to develop new strategies for assessing the potential toxicity of multiple pesticide residues in food. Component-based approaches (see **section 4.3.1, 4.3.2**) have been proposed to address combined toxicity of pesticide mixtures such as **Common Mechanism Groups (CMGs)** in the US<sup>47</sup> and **Cumulative Assessment Groups (CAGs)** in the EU (EFSA, 2013b):

##### I. Common Mechanism Groups (USEPA)

The US Environmental Protection Agency (USEPA) has established 5 CMGs based on 'common mechanism of action' under the FQPA (1996) (see **Appendix IV, Table 3**). The new guidance (USEPA, 2016) acknowledges that more groups may need to be established, which has led the Agency to develop a

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<sup>45</sup> The TTC represents a maximum "safe" exposure threshold value for (groups of) chemicals below which there would be no appreciable human health risk. Munroe et al. (1996) refined the TTC based on the Cramer structural categories system (Class I, II, III) and derived new default safe doses (1800, 540 and 90 µg/person/day for Class I, II, III, respectively) (Barlow, 2005).

<sup>46</sup> The MCR is the ratio between the toxicity of the mixture (based on dose addition models) and the toxicity of the major contributing chemical in the mixture (Kienzler et al., 2016).

<sup>47</sup> <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework>

framework for screening analysis based on MoAs and a weight-of-evidence approach, which builds on the work from the WHO/IPCS (Meek et al., 2011). Three outcomes can be envisaged: (i) no further cumulative assessment work necessary; (ii) a candidate CMG group can be established; (iii) sufficient information exists for establishing key events and CMG).

## II. Cumulative Assessment Groups (EFSA)

As a step towards the implementation of the legal provisions laid down in Regulation (EC) 396/2005 (see **Appendix II**) to address cumulative and synergistic effects of pesticides when setting Maximum Residue Levels (MRLs) (see **section 5.2**), the European Food Safety Authority (EFSA) was requested by the European Commission in 2004 to take the lead and develop the corresponding methods<sup>48</sup>. Since then, EFSA has issued many scientific opinions and developed tools and assessment procedures for conducting cumulative risk assessment of pesticides in food. Major breakthroughs are summarized below (for a more complete overview, see EFSA publications under **references**):

- Building initially on the methodologies developed by the USEPA on the basis of the concept of *dose addition* (e.g. Hazard Index, Point of Departure Index, Relative Potency Factor) (EFSA 2007, 2008), EFSA developed probabilistic approaches for cumulative risk calculation on groups of pesticides (CAGs) for which effects are assumed to be additive, based on the idea that pesticides causing similar toxic effects at different levels of biological organization can produce joint, cumulative toxicity even if they do not have similar MoAs. When knowledge on toxicity of groups of pesticides or similar groups of pesticides is limited, this information is then used to predict the possible combined toxic effects of the chemicals in the group. A tiered approach strategy to grouping has been proposed (CAG level 1 to CAG level 4)<sup>49</sup>. The proof of concept was established with triazole fungicides (EFSA, 2009) for common MoA, and CAGs level 1 and 2 were then proposed for neurotoxic and thyroid effects (EFSA, 2013b), while work was pursued in parallel on pesticides with dissimilar MoA (Kortenkamp et al., 2012; EFSA, 2013c).

Beside hazard-based models, exposure-based models have been also developed, e.g. in the context of dietary exposure assessment. A web-based online tool developed by the EU FP6 project ACROPOLIS is currently being tested for its suitability for carrying out cumulative exposure assessments of multiple pesticide residues for future regulatory purposes<sup>50</sup>.

<sup>48</sup> [http://europa.eu/rapid/press-release\\_IP-04-1485\\_en.htm?locale=en](http://europa.eu/rapid/press-release_IP-04-1485_en.htm?locale=en)

<sup>49</sup> CAG level 1: Toxicological target organ; CAG level 2: Common specific phenomenological effect; CAG level 3: Common mode of action; CAG level 4: Common mechanism of action.

<sup>50</sup> [https://www.rivm.nl/en/Topics/F/Food\\_safety/EFSA\\_RIVM\\_Partnership](https://www.rivm.nl/en/Topics/F/Food_safety/EFSA_RIVM_Partnership)

## 5 Exposure to mixtures of pesticide residues

### 5.1 What are the main sources of exposure to pesticide residues for the general population?

The general population may be exposed to pesticide residues primarily via the diet (including drinking water) and air, and to a minor extent through dermal contact, when:

- Consuming food commodities from animal and plant origin, or drinking water and other beverages containing pesticide residues;
- Via inhalation or dermal contact with spray and vapour drifts (bystanders, residents) when standing near fields treated with plant protection products;
- Coming into direct contact when handling (application, storage, disposal) plant protection products through certain recreational activities such as gardening or by accident;

Dietary exposure represents by far the most important primary source of exposure for the general population. Exposure during manufacture, transport, application, storage or disposal of PPPs is primarily relevant in the occupational setting (workers, farmers). Small children may be exposed to pesticide residues via transfer from hand-to-mouth and object-to-mouth activities in residential gardens or playgrounds as well as by entry into treated fields.

### 5.2 What are Maximum Residue Levels (MRLs) and how are they set?

The Maximum Residue Level (MRL) is the highest concentration of a pesticide residue that is legally tolerated in or on a given food commodity or animal feed. It is defined for a single active ingredient and its relevant degradation products residues in/on a specific crop. In the EU, Regulation (EC) No 396/2005 regulates and harmonises the setting of MRLs in food and feed. In Switzerland, the Swiss Federal Food Safety and Veterinary Office (FSVO) is responsible for the general assessment of pesticide residues and the setting of new MRLs in food, as well as for the control and enforcement of the Swiss Food laws on MRLs (see **section 5.3**)<sup>51</sup>. The FSVO takes into account several factors when setting MRLs (listed in VPRH, Art.3, par. 2), including whether an MRL has been defined in the EU MRL Regulation and by the Codex Alimentarius Commission in order to prevent trade barriers<sup>52</sup>. Every year new MRLs are set for food commodities of plant and animal origin, and existing MRLs are continuously updated to reflect current scientific knowledge and ensure a high level of safety for the consumers.

The amounts of pesticide residues found in food and feed must be safe for consumers and must be as low as technically feasible, according to Good Agricultural Practice (GAP) and the ALARA ('As Low As Reasonably Achievable') principle. While the MRLs are set by the food authorities, applicants are required to submit as part of the authorization procedure for a plant protection product (PPP) the necessary information documenting (i) the minimum amount necessary to protect a crop (e.g. in term of e.g. quantity, frequency, growth stage of the plant); (ii) the pesticide residue levels remaining on the crop after such treatment<sup>53</sup>, and (iii) the toxicological reference values for the pesticidal active ingredient. When setting an MRL, the intake

<sup>51</sup> SR 817.021.23. Verordnung des EDI über die Höchstgehalte für Pestizidrückstände in oder auf Erzeugnissen pflanzlicher und tierischer Herkunft (VPRH) vom 16. Dezember 2016 (Stand am 1. Mai 2018)

<sup>52</sup> The Codex Alimentarius Commission is an intergovernmental body that sets reference food standards (so-called Codex standards) for the international trade. Codex standards exist currently for more than 100 different pesticides; they are set based on health-based reference values (i.e. acceptable daily intakes, ADI) established by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) for safe pesticide residues intake from food (<http://www.who.int/news-room/fact-sheets/detail/pesticide-residues-in-food>).

<sup>53</sup> [https://ec.europa.eu/food/plant/pesticides/max\\_residue\\_levels/application\\_en](https://ec.europa.eu/food/plant/pesticides/max_residue_levels/application_en)

of residues through all food that may be treated with that pesticide is compared with the acceptable daily intake (ADI)<sup>54</sup> and the acute reference dose (ARfD)<sup>55</sup> for long-term (lifetime) and short-term (24h) intake, respectively, and for all consumer groups. If GAP permits, maximum levels are set lower than health protection would require, in order to minimize exposure<sup>56</sup>. Geographical differences and environmental variations are also taken into account when setting MRLs, e.g. warmer and more humid climates favor pest proliferation and may require more insecticides and fungicides treatment. If the requested MRL could lead to exceedance of a health-based guidance value (e.g. ADI) and is not considered safe for human health, adaptations of the GAP may be necessary in order that residues in crops comply with a lower MRL considered safe. If no safe MRL can be derived and/or no alternative GAP can be implemented, MRLs will be set at the validated lowest residue concentration termed 'lower limit of analytical determination' (LOD). This also applies if the requested uses of the pesticide do not lead to detectable residues, if the pesticide fulfils hazard cut-off criteria (e.g. carcinogenic or reprotoxic properties for CAT 1A and 1B) or if no authorisation for a particular pesticide/crop- combination exists. When a pesticide MRL is not specified in the legislation, a general default MRL (0.01 mg/kg) applies<sup>25</sup>.

It should be noted that the MRL is a trading standard, not a safety limit. In practice however, the concept of MRL is often confused with a health-based guidance value, such as the ADI. Whereas an MRL refers to residues of a single active substance on a specific crop, the ADI conceptually is the human counterpart to the animal NOAEL (with several additional factors to account for uncertainties in extrapolation) and can be seen as equivalent to a toxicological threshold value. Therefore, press releases about pesticide residues on crops that refer to exceedance of MRLs do not automatically imply a human health risk (see **section 6.1**).

## 5.3 How are pesticide residues detected in our food?

### 5.3.1 Who is responsible for planning and conducting official food controls?

With the exceptions of the controls done at the border which are the responsibility of the Swiss Confederation (see below), the official controls are planned and executed by the Swiss Cantons. Various legal instruments in the new Swiss Food legislation<sup>57,58</sup> control implementation. Two types of controls are conducted: (i) sample analyses, to check the levels of pesticide residues in/on food products of plant and animal origin; and (ii) business inspection, to control the processes. This is to ensure that the food legislation is being complied with, and that companies, producers and importers have implemented effective product self-monitoring<sup>59</sup>. Risk management measures in case of non-compliance are the responsibility of the cantons, in collaboration with the Swiss Federal Food Safety and Veterinary Office (FSVO). In case of a safety concern for consumer health, a recall or public warning can be initiated by the FSVO. When dangerous

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<sup>54</sup> The Acceptable Daily Intake (ADI) corresponds to the daily intake of a chemical which, during an entire life time, appears to be without appreciable risk to the health of the consumer (WHO/IPCS, 2009b).

<sup>55</sup> The Acute Reference Dose (ARfD) is an '*estimate of the amount of a substance in food or drinking water, expressed on a body weight basis, that can be ingested in a period of 24h or less without appreciable health risk to the consumer*' (WHO/IPCS, 2009b).

<sup>56</sup> [www.blw.admin.ch/blw/de/home/nachhaltige-produktion/pflanzenschutz/pflanzenschutzmittel/nachhaltige-anwendung-und-risikoreduktion.html](http://www.blw.admin.ch/blw/de/home/nachhaltige-produktion/pflanzenschutz/pflanzenschutzmittel/nachhaltige-anwendung-und-risikoreduktion.html)

<sup>57</sup> SR 817.042. Verordnung über den Vollzug der Lebensmittelgesetzgebung (LMVV) vom 16. Dezember 2016 (Stand am 1. Mai 2018).

<sup>58</sup> SR 817.032. Verordnung über den nationalen Kontrollplan für die Lebensmittelkette und die Gebrauchsgegenstände (NKPV) vom 16. Dezember 2016 (Stand am 1. Mai 2017).

<sup>59</sup> SR 817.02. Lebensmittel- und Gebrauchsgegenständeverordnung (LGV) vom 16. Dezember 2016 (Stand am 1. Mai 2018).

foodstuff may have been distributed abroad, the FSVO can report such cases e.g. to the EU *Rapid Alert System for Food and Feed* (RASFF)<sup>60</sup> (see **section 5.4.2**).

### **5.3.2 What types of controls are conducted in Switzerland to detect pesticide residues?**

The Swiss Confederation is responsible for the control of food products at the borders, whereas the cantonal food control authorities are responsible for controls in the country<sup>61</sup>.

At the borders, the Swiss Federal Food Safety and Veterinary Office (FSVO) conducts one annual control programme for foods of plant origin and one for foods of animal origin in collaboration with the Federal customs administration and the cantonal food control authorities and the border veterinary service, respectively. Identification of relevant food products is risk-based and takes into account various factors (e.g. imported volumes, hazard, potential health risks, information from the previous years and from the RASFF<sup>60</sup>, technical feasibility) through a consultation process with all the authorities involved (FSVO, 2017). An Excel-based prioritization tool is used to decide how many samples should be taken for each individual food product.

Within Switzerland, the cantonal authorities are responsible for the control of pesticide residues in/on foods of plant and of animal origin, and for inspecting companies. These controls are carried out throughout the year and the results are published annually by the FSVO. They are included within a specific chapter of the report "*Übersicht amtliche Kontrolle*". This chapter summarizes data from all Swiss official programmes for pesticides in/on foods.

The *National Program for Foreign Substance Detection* (NFUP) in foods of animal origin from Swiss production is conducted annually by the FSVO in collaboration with cantonal authorities. The distribution of samples to be analyzed by the FSVO takes into account the situation prevailing in Switzerland for each animal species/foodstuff and group of substances, and the results of previous years and experience by other countries. This programme, based on EU Directive 96/23, mostly targets residues of veterinary drugs but also includes some pesticide residues (carbamates, chlorinated pesticides).

### **5.3.3 How are the sampling and analysis procedures carried out?**

Food control authorities examine throughout the year a large number of food samples for pesticide residues to ensure the legal conformity of imported and domestically produced foodstuffs. Samples of food from animal or plant origin are collected at the border by the federal customs administration and the border veterinary service, or within the country by the cantonal food control authorities. These controls are executed without notice, as part of e.g. planned and coordinated campaigns; and targeted to specific food commodities, based on suspicion, or following an express order from the competent authority. Results are then transmitted to the Swiss Federal Food Safety and Veterinary Office (FSVO) for further assessment at national level. The number of pesticide residues detected in our food has increased over time; this is due to the technical progress in developing analytical methods with higher sensitivity which are able to detect an increasing number of substances in ever smaller quantities. Food safety authorities are continuously improving the effectiveness of sampling and monitoring of pesticides in food and feed to better address emerging issues, new threats, and public concern.

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<sup>60</sup> [https://ec.europa.eu/food/safety/rasff\\_en](https://ec.europa.eu/food/safety/rasff_en). RASFF participating countries include EU member States, Norway and Liechtenstein.

<sup>61</sup> [www.blv.admin.ch/blv/de/home/lebensmittel-und-ernaehrung/lebensmittelsicherheit/verantwortlichkeiten/nationale-kontrollprogramme.html](http://www.blv.admin.ch/blv/de/home/lebensmittel-und-ernaehrung/lebensmittelsicherheit/verantwortlichkeiten/nationale-kontrollprogramme.html)

## 5.4 What do we know about pesticide residues in food in Switzerland?

Monitoring surveys in Europe and Switzerland demonstrate that low levels of exposure are expected from pesticide residues in food. EU monitoring surveys in 2014 and 2015 showed that 97.1% and 97.2% of the samples analyzed, respectively, were within legal limits; for the samples from non-EU countries only, the proportion of non-compliant samples was 6.5% and 5.6%<sup>62</sup>. For organic farming products, 98.8% and 99.3% of the samples, respectively, were either free of residues or contained residues within legal limits. Official controls show that food of animal and plant origin produced in Switzerland have a very high rate of compliance and is safe for the consumers. Recent results from Swiss national programmes and campaigns carried out in the country in 2015 and 2016 showed that 98% and 99% of the samples analyzed in foods of animal and plant origin, respectively, were free of pesticide residues or contained residues within legal limits (BLV, 2017b; OSAV, 2015). The situation can be quite different for food products imported from non-EU countries, in particular Asiatic countries (e.g. Vietnam, Thailand). In the framework of risk-based campaigns, imported, fresh vegetables and fruits have been recurrently found since 2012 to contain high concentrations of pesticide residues, with an average of ca. one sample out of three exceeding (sometimes even largely) legal limits (OSAV, 2016, 2017; BLV, 2018).

### 5.4.1 What is the situation for food collected in the country?

In 2016, controls in food of animal origin carried out by the Swiss Federal Food Safety and Veterinary Office (FSVO) as part of the *National Program for Foreign Substance Detection* (NFUP) showed that 99.9% of the samples were free of pesticide residues or contained residues within legal limits (BLV, 2017b). Of the 801 samples (meat, fish, milk, eggs, honey) analyzed, only 1 sample (rabbit liver) was non-compliant due to elevated concentrations of *dieldrin* (a banned organochlorine insecticide). It was concluded that the *dieldrin* residues likely originated from the protective glazing of old hutches. In 2015, official controls carried out by the cantonal authorities revealed that out of 1060 samples analyzed from products of Swiss origin, 22 (2%) were assessed as non-compliant. These samples consisted mainly of pears (7 cases), cherries (6 cases) and berries (4 cases). When considering in addition samples (n=1293) from EU and non-EU countries<sup>63</sup>, 1723 (73.2%) samples contained measurable residues within acceptable limits in compliance with legislation, 200 (8.5%) samples were non-compliant, and 430 (18.3%) samples contained no measurable residues (OSAV, 2015). Regarding organic farming products, 94% of the 215 samples analyzed were within legal limits. Of the remaining 6% (n=13), all samples were assessed as non-compliant; 1 sample of dried pears was of Swiss origin, the others (n=12) originated from EU and non-EU countries. These results are fairly comparable to the 2014 situation.

### 5.4.2 What is the situation for food collected at the borders?

Specific programmes and campaigns are regularly conducted at the borders by the custom administration, often based on known risks from previous years, or based on suspicion for specific groups or types products (OSAV, 2016, 2017; BLV, 2017b, 2018). Of the 883 samples of fresh vegetables and spices imported from Asia that were collected at the borders and analyzed between 2012 and 2015, 610 (69%) were free of residues or had residue concentrations within legal limits. The remaining 273 (31%) samples did not meet the legal requirements; of these, 239 (27%) samples were categorized as diminished in value because residue levels were exceeding legal limits, and 34 (4%) samples exceeded the Acute Reference Dose (ARfD), i.e. a health risk to consumers could not be excluded. The analyses revealed 221 different pesticides, of which 102 (46%) exceeded the maximal concentration or are not authorized in Switzerland. Of these pesticides, 29 (13%)

<sup>62</sup> [www.efsa.europa.eu/en/press/news/161026](http://www.efsa.europa.eu/en/press/news/161026); <http://www.efsa.europa.eu/en/press/news/170411>

<sup>63</sup> For the year 2015, a total of 2353 samples were collected and analyzed, 1060 samples were from a Swiss origin, 1293 samples were from EU and non-EU countries (i.e. Asia, Africa, South America, and North America) (OSAV, 2015).

exceeded the ARfD (OSAV, 2016). These results show the need for continuous and reinforced food controls for fresh vegetables and fruits from Asia (on average ca. 30% of samples non-compliant, but as high as 60% in some instances e.g. for products from Vietnam) or tea from Asia and Africa (10% of samples non-compliant), as shown in the 2016 and 2017 campaigns (BLV, 2017b, 2018). In several instances, the pesticide residues levels detected were so high that they even exceeded the ARfD, therefore potentially posing an acute health risk to the consumer. Several pesticides detected were banned in Switzerland and the EU (e.g. *profenofos* and *acephate*, two organophosphate insecticides). Failure to respect Good Agricultural Practice (GAP) and different use patterns in the country of origin may explain these results. The Swiss Federal Food Safety and Veterinary Office (FSVO) has taken steps to reinforce controls at the borders from 1 May 2020<sup>64</sup>. The cantons have also an important role to play as they must also systematically ensure that the responsible importers carry out the self-checks to which they are held.

## 5.5 Are there specific mixtures of pesticide residues to which the Swiss population is exposed to?

It is difficult to define specific or standard type of pesticide mixtures on a population or an individual level. Environmental exposures to coincidental mixtures of pesticides are always changing in term of their combinations and concentrations; therefore, individual exposures will vary for each individual, depending on his/her activities, occupation, residence area, and consumption habits, among other factors. With regard to dietary exposure, consumers are exposed to multiple residues in and on our food, in drinking water and beverages. Personal habits can contribute to reduce the levels of residues in food, e.g. washing, peeling and cooking foodstuffs. Similarly, pesticide residues are usually reduced during storage and commercial processing.

The PSMV lists up to 357 single active pesticidal ingredients that are authorized for use in plant protection products (PPPs) in Switzerland<sup>65</sup>. Swiss consumers, however, not only eat food produced locally, but also imported food produced in EU and non-EU countries<sup>66</sup>. Imported foodstuff from non-EU countries may also contain PPP residues that are not allowed in Switzerland and in the EU, most notably in fresh vegetables and spices imported from Asia (BLV, 2016, 2017, 2018). While information can be obtained (biomonitoring) on the total sum of pesticides a person was exposed to in a given timeframe (certain PPPs accumulate more than others in the human body), this reflects exposure from all sources; however, specific sources of exposure cannot be identified, and it is not possible to determine to which specific mixtures this person was exposed to and from which origin.

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<sup>64</sup> The legal basis is the new LMVV, SR 817.042. Verordnung über den Vollzug der Lebensmittelgesetzgebung (LMVV) vom 16. Dezember 2016 (Stand am 1. Mai 2018), Art. 56 sq., in accordance to the Regulation (EC) 669/2009 and Implementing Regulation (EU) 884/2014.

<sup>65</sup> See Anhang I, Teil A: Chemische Stoffe zur Verwendung in Pflanzenschutzmitteln. PSMV, SR 916.161. Verordnung über das Inverkehrbringen von Pflanzenschutzmitteln (Pflanzenschutzmittelverordnung, PSMV) vom 12. Mai 2010 (Stand am 1. Januar 2018).

<sup>66</sup> In international comparison, Switzerland has one of the lowest coverage of food requirements by domestic production; circa 50% of the food consumed in Switzerland is imported, of which more than 60% comes from the EU (SBV, 2015, 2018).

## 6 Health risks from mixtures of pesticide residues in food

Pesticides have potent chemical and biological properties which could be harmful to humans, and are therefore strictly regulated (see **section 3**). Pesticide regulations covering the placing of pesticides on the market and for setting Maximum Residue Levels (MRLs) in food stipulate that pesticides should have no harmful effects – including cumulative and synergistic effects – on humans. The notion of risk entails two parts, i.e. *hazard* (the intrinsic toxicity of a chemical which will lead to certain effects in an individual at a sufficiently high dose, see **section 4**) and *exposure* (the quantity of the chemical that this individual will effectively be exposed to, see **section 5**). A pesticide cannot be authorized for use if it has genotoxic, mutagenic or carcinogenic properties, or if it has toxic effects on fertility and/or reproduction of a higher degree (i.e. if it belongs to the CAT. 1 CMR), or if it is shown to be an endocrine disruptor. Only pesticides classified as CAT. 2 CMR can be authorized if the exposure has been proven to be negligible (PMSV; EC/1107/2009, Annex II, point 3). Considerable efforts have been and are currently invested to develop hazard-based criteria for identification of endocrine disrupting chemicals under PPP Regulation (EC) 1107/2009. Pesticides are authorized with respect to their intended use under reasonably foreseeable conditions. When people come into contact with large quantities of pesticide (*high dose exposure*), as it may occur e.g. accidentally in the occupational setting, this may cause acute poisoning or long-term health effects. As a general rule, the potential occurrence of adverse health effects from pesticide mixtures must be assessed on a case-by-case basis.

### 6.1 What are the health risks associated with multiple pesticide residues from the diet?

Consumers are exposed orally to very small amounts of multiple pesticide residues via food and drinking water (*low dose exposure*); these levels are required to be below the effective doses for toxicity. The current view is that interactions (as defined in **Table 2**) between pesticide residues, such as synergy, are not expected to occur regularly at dietary exposure levels. Current scientific evidence suggests that exposure to mixtures of multiple pesticide residues is unlikely to represent a potential concern for human health, provided that each mixture component is well regulated based on established risk assessment approaches (i.e. health-based reference values such as the Acceptable Daily Intake (ADI) or the Acute Reference Dose (ARfD), maximum allowable concentrations in drinking water, Maximum Residue Levels). Humans are continuously exposed to traces of a large number of chemicals without suffering adverse health effects. However, depending on their food consumption habits, consumers may be exposed to levels of individual pesticide residues that exceed the ARfD, as shown for imported foodstuff from non-EU countries (see **section 5.4**). In these circumstances, a single or short-term exceedance of the ADI may represent a health risk to the consumers (BfR, 2015). In conclusion, the health risks from pesticide residues to consumers via food and drinking water remains low, both in the short-term and long-term, a position that is held by all major food safety authorities worldwide, including by the Swiss Federal Food Safety and Veterinary Office (FSVO).

#### 6.1.1 Why exceedance of the MRLs does not automatically constitute a health risk for consumers?

Food safety authorities are responsible for consumer safety and evaluating potential health risks that may arise from dietary exposure to pesticides, taking into account the toxicity of the individual active ingredient (*hazard*), the maximum pesticide levels expected on food, and the different diets of the population (*exposure*). When setting a Maximum Residue Level (MRL, see **section 5.2**), the intake of pesticide residues through all food that may be treated with that pesticide is compared with the Acceptable Daily Intake (ADI) or the Acute Reference Dose (ARfD) for long and short-term intake and for all consumer groups (see **section 6.2**). It should be noticed that MRLs are not health-based reference values or safety limits, but trading standards (see **section 5.2**); exceedance does not necessarily imply a risk for public or animal health, as often suggested in the media and public discourse, which tends to confuse the concept of MRL with that of health-

based reference values. MRLs are proposed based on GAP and ALARA principles, and are set only if acceptable in terms of human health, taking into account vulnerable groups of the population (see **section 5.2** and **section 6.3**).

## 6.2 Are there groups at higher risk in the general population?

Generally speaking, the most at-risk population consists of the people who are directly exposed to pesticides primarily in the occupational setting, such as agricultural workers during manufacture, transport, application, storage, and disposal activities. Other people may be exposed to pesticide drifts when standing in the immediate area (bystanders) or when living close to agricultural fields (residents) during and immediately after pesticides are applied. Gardening may be an additional source of exposure in the residential setting. For the general population not living in areas where pesticide use is widespread, however, exposure to pesticides is significantly lower and occurs primarily through the diet (see **section 5.1**). In the general population, unborn children, babies and small children may be particularly vulnerable subgroups for certain compounds, for example, when considering potential neurodevelopmental and neurobehavioral effects of organophosphate pesticides. Other vulnerable groups may be defined on the basis of specific dietary habits which may increase their exposure e.g. raw or semi-processed foods such as fruits, vegetables, seeds, etc. that may contain higher pesticide residue levels than other food groups such as dairy products or meat. Therefore, vulnerable groups in the population need to be defined with regard to hazard and exposure, in a specific risk assessment context. The notion of vulnerability is covered by the European and Swiss legislations on plant protection products. The Swiss Ordinance on Plant Protection Products (PSMV) defines vulnerable groups as: '*people who need special attention in the context of the assessment of the acute and chronic effects of plant protection products on health. These groups include pregnant and lactating women, unborn children, infants and children, the elderly, and workers and residents who are highly exposed to pesticides over the long term*' (PSMV, art. 3, let. m).

Food safety authorities such as the Swiss Federal Food Safety and Veterinary Office (FSVO) or EFSA verify that pesticide residues are safe for all consumers, particularly for vulnerable groups within the population; the latter are taken into account when setting MRLs. For example, children consume relatively more apple juice than adults and the Maximum Residue Level (MRL) is therefore set to ensure that safe levels will not be exceeded even with a high level of consumption (BfR, 2015). If a risk is established for any consumer group, food safety authorities take immediate action to set MRLs at a lower level (as low as technically feasible) or can reject the authorization to use a pesticide on a given crop (see **section 5.2**). Consumer safety has always precedence over plant protection. The European Food Safety Authority (EFSA) has just recently made a number of recommendations to further protect young infants from potential risks posed by multiple pesticide residues in food (EFSA, 2018b).

### 6.3 What action has been taken at science and policy level with regard to chemical mixtures?

Intense efforts have been and are currently being made at EU level for developing new approaches and tools to better address the potential impact of chemical mixtures on public and animal health as well as on the environment. Action has already been taken in recent years through national and international, multi-sector, multi-stakeholder research programmes (ACROPOLIS<sup>67</sup>; EuroMix<sup>68</sup>; EDC-MixRisk<sup>69</sup>; EU-ToxRisk<sup>70</sup>; HBM4EU<sup>71</sup>; SOLUTIONS<sup>72</sup>), scientific activities (ECETOC, 2012; JRC, 2014, 2018; HESI RISK21 project, Solomon et al., 2016; Moretto et al., 2017), regulatory initiatives (WHO/IPCS, 2009a; OECD, 2011; EC, 2012a; EFSA, 2008, 2018a), and multiple events and scientific workshops to address the challenges of chemical mixture risk assessment and future priorities on the topic (e.g. EFSA, 2007; WHO, 2009a; EuroMix, 2018;<sup>73,74</sup>). The recommendations from the European Commission for setting research and regulatory priorities (EC, 2012a) have resulted in a corresponding science and policy agenda (EC, 2012b), with the European Food Safety Authority (EFSA) taking the lead in the area of mixture risk assessment of pesticide residues in the food chain.

#### 6.3.1 What research efforts are being dedicated to study the combined effects of pesticide mixtures?

The European Food Safety Authority (EFSA) is at the forefront of ongoing research in various areas such as hazard, exposure and risk related activities, data collection and harmonisation. These efforts are part of a general strategy outlined by the European Commission (EC, 2012b) which relies on four major cornerstones:

- I. Identify chemical mixtures of potential concern for risk assessment
  - Develop hazard and exposure-based criteria for prioritization; identification of lower thresholds for synergistic effects → *ongoing at EFSA*
  - Establish a list of substances of concern, including co-formulants (e.g. tallowamine in glyphosate-based formulations) → *OFAG in collaboration with other EU chemical regulatory bodies*
- II. Improve data availability, collection and analysis
  - Collect mode of action (MoA) data to support grouping; collection of TK/TD data; collection of exposure data at realistic low doses → *ongoing at EFSA (EFSA 2015b, 2015c)*
- III. Develop new tools and methods for toxicity testing and risk assessment of chemical mixtures
  - Further establish common assessment group (CAG) methodology and expand application of the AOP framework, integrated testing strategies and PBTK modeling → *ongoing at EFSA (EFSA 2013b, 2014, 2016; EFSA 2018c)*

<sup>67</sup> A web-based online tool was developed by the EU FP6 project ACROPOLIS using a probabilistic Monte Carlo Risk Assessment (MCRA) models for the probabilistic calculation of the pesticide exposure levels distribution within a population. [https://www.rivm.nl/en/Topics/F/Food\\_safety/EFSA\\_RIVM\\_Partnership](https://www.rivm.nl/en/Topics/F/Food_safety/EFSA_RIVM_Partnership)

<sup>68</sup> Horizon 2020 funded project on tiered strategies for risk assessment of mixtures of multiple chemicals, <http://www.euromixproject.eu>

<sup>69</sup> Horizon 2020 funded project focusing on the effects of mixtures of endocrine disruptors on children, <http://edcmixrisk.ki.se/>

<sup>70</sup> Horizon 2020 funded project on chemical mixture assessment for alternatives to animal testing, <http://www.eu-toxrisk.eu/>

<sup>71</sup> Horizon 2020 funded project on human health risk assessment of chemical mixtures, <https://www.hbm4eu.eu/>

<sup>72</sup> FP7 funded project on environmental impact of chemical mixtures, <https://www.solutions-project.eu/>

<sup>73</sup> EFSA-RIVM Symposium 'The future of risk assessment and toxicity testing for chemical mixtures', 18-19 May 2016, Utrecht, The Netherlands, [www.rivm.nl/en/Topics/F/Food\\_safety/EFSA\\_RIVM\\_Symposium](https://www.rivm.nl/en/Topics/F/Food_safety/EFSA_RIVM_Symposium)

<sup>74</sup> Joint Horizon 2020 Workshop 'Advancing the Assessment of Chemical Mixtures and their Risks for Human Health and the Environment', 29-30 May 2018, JRC, Ispra, Italy, <https://ec.europa.eu/jrc/en/news/chemical-mixtures-safety>

#### IV. Develop harmonised terminology and procedures across sectorial chemical legislations

- Improve cross-sectorial consistency, technical convergence and harmonisation of data collection, use across human and ecological risk assessment → *ongoing at EFSA (EFSA 2015a; 2018d)*

As part of the EU-funded project ACROPOLIS, EFSA has developed, in partnership with the Dutch National Institute for Public Health and the Environment (RIVM), a software tool<sup>66</sup> for the calculation of cumulative exposure to pesticides residues (EFSA, 2016). This tool is currently being tested in two pilot studies for carrying out exposure assessments of multiple pesticide residues (EFSA 2018a) to support EFSA annual reporting on pesticides residues in food and, once more experience is gained, to use these tools for regulatory mixture risk assessment purposes (e.g. in the context of regulatory decisions on applications concerning pesticide MRLs in food). The two pilot assessments which use the tool on groups of pesticides targeting the human nervous and thyroid systems are expected to be finalized by the end of 2018. In the coming years, EFSA plans to further establish its CAG methodology (2013b) and to add CAGs for other organs, tissues and systems such as the liver, kidneys, eyes, the hematopoietic system and bone, and the reproductive and developmental systems. Data is already being collected to define groups of pesticides that target these systems<sup>75</sup>.

On 28 June 2018, EFSA has launched two public consultations on draft guidance<sup>76</sup> and a draft statement<sup>77</sup> in relation to chemical mixtures hazard and risk assessment:

- **Draft EFSA Guidance on Harmonised Methodologies for Human Health, Animal Health and Environmental Risk Assessment of Combined Exposure to Multiple Chemicals (2018c):**

EFSA has been developing a guidance document on harmonised methodologies for human health, animal health, and ecological risk assessment of combined exposure to multiple chemicals. Aimed at the food and feed safety areas, the draft guidance can be applied to other regulatory areas as well. A harmonised framework for chemical mixture risk assessment is proposed; it features all the classical steps of a risk assessment (including problem formulation) and uncertainty analysis, and offers flexibility in using qualitative, semi-quantitative or fully probabilistic methodologies, depending on the risk assessment context, time and resources constraints. The framework proposes tiered and stepwise approaches for both **whole mixture** approaches and **component-based** approaches. Specific considerations are given to component-based approaches including: (i) the grouping of chemicals into common assessment groups; (ii) the use of dose addition as a default assumption; (iii) approaches to integrate evidence of interactions; and (iv) the refinement of assessment groups.

- **Draft EFSA Statement on Genotoxicity Assessment of Chemical Mixtures (2018d):**

Building on its draft '*Guidance on harmonised risk assessment methodologies for human health, animal health and ecological risk assessment of combined exposure to multiple chemicals*' (EFSA, 2018c), the document focuses on specific considerations to be addressed when conducting a genotoxicity assessment of chemical mixtures. It builds on the working definition of chemical mixtures (EFSA, 2018c) and proposes to differentiate between simple and complex mixtures, depending on their degree of characterization. Criteria are proposed with regard to classifying simple mixtures and complex mixtures as to whether they are genotoxic or are of no concern with respect to genotoxicity,

<sup>75</sup> <http://www.efsa.europa.eu/en/press/news/180419>

<sup>76</sup> <http://www.efsa.europa.eu/en/consultations/call/180626-0>

<sup>77</sup> <http://www.efsa.europa.eu/en/consultations/call/180626>

taking into account the component-based and whole mixture approaches, together with a tiered approach testing strategy in vitro and in vivo.

### **6.3.2 What regulatory solutions are being proposed to address the combined effects of pesticide mixtures?**

At EU level, many of the FP7 and Horizon 2020 research projects dedicated to combined effects of chemical mixtures are working together to identify remaining gaps in mixture research and policy. Their progress is being closely monitored by the Commission services and EU agencies (EFSA, ECHA, EMA, EEA) in order to best translate science into regulatory risk assessment practice and decision-making. The European Commission has already taken steps to: (i) strengthen inter-Agency collaboration and EU research related coordination activities ; (ii) promote a transversal and horizontal approach across the different pieces of sectorial EU chemical legislations; (iii) improve/promote the implementation of new tools and technologies for chemical mixture risk assessment in Europe; (iv) promote (ideally) a systematic, harmonised and integrated approach to chemical mixture risk assessment (in particular regarding priority mixtures); (v) adapt existing legislation to reflect current scientific knowledge and technical progress.

Mechanisms exist for reinforcing the implementation of existing sectorial chemical legislations and assessing whether they are efficient and ‘fit-for-purpose’. Since 2016, the European Commission has been conducting an evaluation of the PPP and MRL Regulations to assess their level of application, their impact, and whether they adequately meet the needs of the population, industry and public institutions.

For both chemicals and pesticides, this requires a long-term vision of risk governance and prioritization setting in EU Health and Environment strategy and policy (e.g. Strategy for a Non-Toxic Environment<sup>78</sup>, Directive for a Sustainable Use of Pesticides<sup>79</sup>, National Action Plans<sup>80,81</sup>), but also long-term efforts in capacity building and funding to allocate the corresponding resources.

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<sup>78</sup> [http://ec.europa.eu/environment/chemicals/non-toxic/index\\_en.htm](http://ec.europa.eu/environment/chemicals/non-toxic/index_en.htm)

<sup>79</sup> Directive 2009/128/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for Community action to achieve the sustainable use of pesticides (Text with EEA relevance) OJ L 309.

<sup>80</sup> <https://www.blw.admin.ch/blw/de/home/nachhaltige-produktion/pflanzenschutz/aktionsplan.html>;

<sup>81</sup> [https://ec.europa.eu/food/plant/pesticides/sustainable\\_use\\_pesticides/nap\\_en](https://ec.europa.eu/food/plant/pesticides/sustainable_use_pesticides/nap_en)

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## Appendix I – Methodology for the rapid scoping review and literature search

### 1. Scoping: cocktail effects of pesticide mixtures in the media (CH<sup>1-4</sup>, EU<sup>5-29</sup>, US<sup>30-34</sup>)

- <sup>1</sup> <https://www.rts.ch/play/tv/a-bon-entendeur/video/les-residus-de-pesticides-et-leur-consequence-sur-la-sante?id=3091371>
- <sup>2</sup> <https://www.bonasavoir.ch/918991-test-15-paquets-de-spaghettis-traces-de-pesticides-toxiques>
- <sup>3</sup> <https://www.srf.ch/news/panorama/pestizide-in-nahrungsmitteln-wie-gefaehrlich-sind-die-rueckstaende-in-unserem-essen>
- <sup>4</sup> <https://www.gesundheitstipp.ch/artikel/d/pestizid-cocktail-in-der-pink-lady/>
- <sup>5</sup> [https://www.sciencesetavenir.fr/sante/maladie-enfant/un-cocktail-de-pesticides-retrouve-dans-les-cheveux-des-enfants\\_14791](https://www.sciencesetavenir.fr/sante/maladie-enfant/un-cocktail-de-pesticides-retrouve-dans-les-cheveux-des-enfants_14791)
- <sup>6</sup> [https://www.francetvinfo.fr/sante/environnement-et-sante/effets-cocktail-le-defi-scientifique-des-interactions-chimiques-inattendues\\_1068113.html](https://www.francetvinfo.fr/sante/environnement-et-sante/effets-cocktail-le-defi-scientifique-des-interactions-chimiques-inattendues_1068113.html)
- <sup>7</sup> [http://www.lemonde.fr/planete/article/2012/08/07/l-inquietant-effet-cocktail-des-pesticides-sur-nos-cellules\\_1743277\\_3244.html](http://www.lemonde.fr/planete/article/2012/08/07/l-inquietant-effet-cocktail-des-pesticides-sur-nos-cellules_1743277_3244.html)
- <sup>8</sup> [http://www.lemonde.fr/planete/article/2017/09/15/perturbateurs-endocriniens-un-cocktail-toxique-pour-l-homme\\_5186430\\_3244.html](http://www.lemonde.fr/planete/article/2017/09/15/perturbateurs-endocriniens-un-cocktail-toxique-pour-l-homme_5186430_3244.html)
- <sup>9</sup> [http://www.liberation.fr/sciences/2015/09/03/une-etude-revele-la-dangerosite-de-l-effet-cocktail-des-molecules\\_1374910](http://www.liberation.fr/sciences/2015/09/03/une-etude-revele-la-dangerosite-de-l-effet-cocktail-des-molecules_1374910)
- <sup>10</sup> <http://www.20minutes.fr/societe/1942675-20161014-pesticides-tout-comprendre-effet-cocktail>
- <sup>11</sup> <http://generations-futures.blogspot.ch/>
- <sup>12</sup> <http://www.menustoquiques.fr/sciences-menus-toxiques-generations-futures.html>
- <sup>13</sup> <https://www.alternatives-economiques.fr/pesticides-gare-a-leffet-cocktail/00045405>
- <sup>14</sup> <http://www.rfi.fr/science/20170914-sante-perturbateurs-endocriniens-foetus-effet-cocktail>
- <sup>15</sup> <http://barbalabs.com/effet-cocktail-et-pesticides-ce-qu'en-pense-la-science-perturbateurs-endocriniens/>
- <sup>16</sup> [http://controverses.mines-paristech.fr/public/promo15/promo15\\_G19/www.controverses-minesparistech-4.fr/\\_groupe19/effet-cocktail/index.html](http://controverses.mines-paristech.fr/public/promo15/promo15_G19/www.controverses-minesparistech-4.fr/_groupe19/effet-cocktail/index.html)
- <sup>17</sup> <http://www.spppi-paca.org/a/118/effets-cocktails-melanges-o-en-est-la-recherche-/>
- <sup>18</sup> <http://seppi.over-blog.com/2017/05/l-effet-cocktail-du-monde-et-de-generations-futures-sur-agriculture-et-environnement.html>
- <sup>19</sup> <https://www.actu-environnement.com/ae/news/insrm-perturbateurs-endocriniens-effet-cocktail-29650.php4>
- <sup>20</sup> <https://www.focus.de/gesundheit/ernaehrung/news/greenpeace-test-obst-und-gemuese-oft-mit-pestizid-cocktail ueberfrachtet aid 728092.html>
- <sup>21</sup> <https://weserreport.de/2016/07/delmenhorst/lafu-untersucht-salate-fuer-verbrauchersendung/>
- <sup>22</sup> <https://help.orf.at/stories/2811905/>
- <sup>23</sup> <http://www.pan-uk.org/food-for-thought/>
- <sup>24</sup> <https://theecologist.org/2017/sep/05/cocktail-pesticide-residues-fruit-and-vegetables-given-schoolchildren>
- <sup>25</sup> <https://www.riverford.co.uk/blog/2017/04/21/quays-news-i-dont-trust-regulation-pesticides/>
- <sup>26</sup> <https://www.lifegate.it/persone/news/un-cocktail-di-pesticidi-per-le-nostre-tavole>

<sup>27</sup> <https://ilsalvagente.it/2016/01/29/lefsa-scopre-leffetto-cocktail-dei-pesticidi/>

<sup>28</sup> [http://www.repubblica.it/ambiente/2015/01/08/news/ispra\\_pesticidi-104526067/](http://www.repubblica.it/ambiente/2015/01/08/news/ispra_pesticidi-104526067/)

<sup>29</sup> <http://www.greenpeace.org/eu-unit/en/News/2017/EU-report-on-pesticide-residues-ignores-toxic-cocktail-effect-Greenpeace/>

<sup>30</sup> <https://www.sciencedaily.com/releases/2017/12/171213104938.htm>

<sup>31</sup> <https://www.ecowatch.com/how-the-epa-ignores-the-dangers-of-pesticide-cocktails-1933975259.html>

<sup>32</sup> <https://www.naturalnews.com/2018-01-02-chemical-cocktail-how-pesticides-amplify-chemical-damage-environment.html>

<sup>33</sup> <https://globaljusticeecology.org/scientists-our-food-is-being-sprayed-by-toxic-chemical-cocktail/>

<sup>34</sup> <https://www.alkaway.com.au/blog/efsa-ignores-cocktail-effect-of-multiple-pesticide-residues-in-food/>

## 2. Scoping: combined effects of pesticide mixtures, regulatory perspective (CH<sup>1-3</sup>, EU<sup>4-10</sup>, US & International<sup>11-14</sup>)

<sup>1</sup> OFAG [www.blw.admin.ch/blw/de/home/nachhaltige-produktion/pflanzenschutz/pflanzenschutzmittel.html](http://www.blw.admin.ch/blw/de/home/nachhaltige-produktion/pflanzenschutz/pflanzenschutzmittel.html)

<sup>2</sup> FSVO [www.blv.admin.ch/blv/de/home/lebensmittel-und-ernaehrung/lebensmittelsicherheit/stoffe-im-fokus/glyphosat.html](http://www.blv.admin.ch/blv/de/home/lebensmittel-und-ernaehrung/lebensmittelsicherheit/stoffe-im-fokus/glyphosat.html)

<sup>3</sup> Swiss Parliament <https://www.parlament.ch/fr/ratsbetrieb/suche-curia-vista/geschaeft?AffairId=20133979>

<sup>4</sup> European Commission [https://ec.europa.eu/food/plant/pesticides/max\\_residue\\_levels/cumulative\\_risk\\_en](https://ec.europa.eu/food/plant/pesticides/max_residue_levels/cumulative_risk_en)

<sup>5</sup> EFSA <https://www.efsa.europa.eu/en/topics/topic/pesticides>

<sup>6</sup> ANSES <https://www.anses.fr/en/content/french-observatory-pesticide-residues>

<sup>7</sup> INSERM <https://www.inserm.fr/information-en-sante/expertises-collectives/pesticides-effets-sur-sante>

<sup>8</sup> INRA <http://www.inra.fr/en/Scientists-Students/Food-and-nutrition/All-reports/Cocktail-effects-of-toxic-substances/The-cocktail-effect-of-pesticides>

<sup>9</sup> BfR [https://www.bfr.bund.de/en/plant\\_protection\\_product\\_residues\\_in\\_food-197984.html](https://www.bfr.bund.de/en/plant_protection_product_residues_in_food-197984.html)

<sup>10</sup> BVL [http://www.bvl.bund.de/DE/04\\_Pflanzenschutzmittel/02\\_Verbraucher/02\\_PSM\\_Rueckstaende\\_LM/psm\\_PSMRueckstaendeLM\\_node.html](http://www.bvl.bund.de/DE/04_Pflanzenschutzmittel/02_Verbraucher/02_PSM_Rueckstaende_LM/psm_PSMRueckstaendeLM_node.html)

<sup>11</sup> USEPA <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides>

<sup>12</sup> WHO <http://www.who.int/news-room/fact-sheets/detail/pesticide-residues-in-food>

<sup>13</sup> FAO/WHO [http://www.who.int/foodsafety/areas\\_work/chemical-risks/jmpr/en/](http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/)

<sup>14</sup> Codex Alimentarius <http://www.fao.org/fao-who-codexalimentarius/thematic-areas/pesticides/en/>

## Appendix II – Provisions for cumulative effects of pesticide mixtures in the EU legislation

### Maximum Residue Levels (MRLs) Regulation (EC 396/2005)

#### *Introduction*

(6) "It is also important to carry out further work to develop a methodology to take into account **cumulative** and **synergistic effects**. In view of human exposure to **combinations of active substances** and their **cumulative** and **possible aggregate** and **synergistic effects** on human health, MRLs should be set after consultation of the European Food Safety Authority (...)".

#### *Art.14, Decisions on applications concerning MRLs*

(2) *With regard to the acts referred to in paragraph 1, account shall be taken of:*

*(b) the possible presence of pesticide residues arising from sources other than current plant protection uses of active substances, and their **known cumulative** and **synergistic effects**, when the methods to assess such effects are available;*

#### *Art.36, Support measures relating to harmonised pesticide MRLs*

(1) *Support measures relating to harmonised pesticide MRLs shall be established at Community level, including:*

*(c) studies and other measures necessary for the preparation and development of legislation and of technical guidelines on pesticide residues, aimed, in particular, at developing and using methods of assessing **aggregate**, **cumulative** and **synergistic effects**;*

### Plant Protection Products Regulation (EC 1107/2009)

#### *Art. 4, Approval criteria for active substances*

(2) *The residues of the plant protection products, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use, shall meet the following requirements:*

*(a) they shall not have any harmful effects on human health, including that of vulnerable groups, or animal health, taking into account **known cumulative** and **synergistic effects** where the scientific methods accepted by the Authority to assess such effects are available (...)".*

(3) *A plant protection product, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use, shall meet the following requirements:*

*(b) it shall have no immediate or delayed harmful effect on human health, including that of vulnerable groups, or animal health, directly or through drinking water (taking into account substances resulting from water treatment), food, feed or air, or consequences in the workplace or through other indirect effects, taking into account **known cumulative** and **synergistic effects** where the scientific methods accepted by the Authority to assess such effects are available (...)".*

### Biocidal Products Regulation (EU 528/2012)

#### *Art. 8, Evaluations of applications*

(3) *Where the evaluating competent authority considers that there are concerns for human health, animal health or the environment as a result of the **cumulative effects** from the use of biocidal products containing the same or different active substances, it shall document its concerns in accordance with the requirements of the*

relevant parts of Section II.3 of Annex XV to Regulation (EC) No 1907/2006 and include this as part of its conclusions.

*Art.19 Conditions for granting an authorization*

(2) *The evaluation of whether a biocidal product fulfils the criteria set out in point (b) of paragraph 1 shall take into account the following factors:*

*(d) cumulative effects;*

*(e) synergistic effects.*

**ANNEX VI COMMON PRINCIPLES FOR THE EVALUATION OF DOSSIERS FOR BIOCIDAL PRODUCTS**

(3) *In order to ensure a high and harmonised level of protection of human health, animal health and the environment, any risks arising from the use of a biocidal product shall be identified. To achieve this, a risk assessment shall be carried out to determine the acceptability or otherwise of any risks that are identified. This is done by carrying out an assessment of the risks associated with the relevant individual components of the biocidal product, taking into account any cumulative and synergistic effects.*

(15) *In carrying out the assessment, the possibility of cumulative or synergistic effects shall also be taken into account. The Agency shall, in collaboration with the Commission, Member States and interested parties, develop and provide further guidance on the scientific definitions and methodologies for the assessment of cumulative and synergistic effects.*

(53) *In each of the areas where risk assessments have been carried out, the evaluating body shall combine the results for the active substance together with the results for any substance of concern to produce an overall assessment for the biocidal product itself. This shall also take account of any cumulative or synergistic effects.*

## Appendix III – Provisions for cumulative effects of pesticide mixtures in the Swiss legislation

### VPRH (SR 817.021.23) Stand am 1. Mai 2018

Art. 3, Kriterien und Grundlagen für die Ermittlung der Rückstandshöchstgehalte

<sup>2</sup> Es [das BLV] berücksichtigt dabei:

- i. die **bekannten kumulativen oder synergistischen Interaktionen** von Wirkstoffen, die auf gleiche biologische Systeme im menschlichen Organismus wirken;

### PSMV (SR 916.161) Stand am 1. Januar 2018

Art. 4, Kriterien

<sup>3</sup> Die Rückstände von Pflanzenschutzmitteln müssen nach der Verwendung entsprechend der guten Pflanzenschutzpraxis und unter realistischen Verwendungsbedingungen folgende Anforderungen erfüllen:

- a. Sie dürfen keine schädlichen Auswirkungen auf die Gesundheit von Menschen, einschliesslich besonders gefährdeter Personengruppen, oder von Tieren – unter Berücksichtigung von **Kumulations- und Synergieeffekten**, wenn es von der Europäischen Behörde für Lebensmittelsicherheit (EFSA) anerkannte wissenschaftliche Methoden zur Messung solcher Effekte gibt (...)

<sup>5</sup> Das Pflanzenschutzmittel muss nach der Verwendung entsprechend der guten Pflanzenschutzpraxis und unter realistischen Verwendungsbedingungen folgende Anforderungen erfüllen:

- b. Es darf keine sofortigen oder verzögerten schädlichen Auswirkungen auf die Gesundheit von Menschen, einschliesslich besonders gefährdeter Personengruppen, oder von Tieren – weder direkt noch über das Trinkwasser (unter Berücksichtigung der bei der Trinkwasserbehandlung entstehenden Produkte), über Nahrungs- oder Futtermittel oder über die Luft oder Auswirkungen am Arbeitsplatz oder durch andere indirekte Effekte unter Berücksichtigung **bekannter Kumulations- und Synergieeffekte**, soweit es von der EFSA anerkannte wissenschaftliche Methoden zur Bewertung solcher Effekte gibt (...)

### VPB (SR 813.12) Stand am 1. März 2018

Art. 11b, Bewertungsfaktoren

Bei der Prüfung, ob ein Biozidprodukt die Voraussetzungen nach Artikel 11 Absatz 1 Buchstabe a erfüllt, werden die folgenden Faktoren berücksichtigt:

- d. **Kumulationseffekte**;
- e. **Synergieeffekte**.

## Appendix IV – Common modes of action for some classes of pesticides

**Table 3: Established common modes of action for some classes of pesticides (CMGs)**

Pesticide category	Chemical class	Active	Index	Mode of action	References
Insecticides	Organophosphates	46	Methamidophos	Long-term/irreversible cholinesterase inhibition	USEPA, 2002
Insecticides	N-methyl carbamates	11	Oxamyl	Reversible cholinesterase inhibition	USEPA, 2006
Herbicides	Triazines		Atrazine, simazine, & metabolites DEA, DIA, DACT; assumed equipotent	CNS modulation of hypothalamic-pituitary-gonadal axis (mammary tumors in rats)	USEPA, 2006
Herbicides	Chloroacetanilides		Acetochlor =0.05, alachlor=1	Nasal olfactory epithelium tumors in rats	USEPA, 2006
Insecticides	Pyrethroids	15	Deltamethrin	Behavioral neurotoxicity in rats	USEPA, 2011

(Source: SCAHT)

Legal basis: The US Food Quality Protection Act (FQPA) for child protection from pesticides requires USEPA to consider 'cumulative exposure' to pesticide residues that have common mechanisms of toxicity (see **section 3.1** and **section 4.3**). Thiocarbamates and dithiocarbamates are excluded because they do not share a common mechanism of toxicity.

## Glossary of terms

<b>Acceptable Daily Intake</b>	<i>The Acceptable Daily Intake (ADI) is an estimate of the amount of a chemical (pesticide residue) in food or drinking-water that can be ingested daily over a lifetime without appreciable health risk to the consumer.. It is expressed in milligrams of the chemical per kilogram of body weight. (WHO/IPCS, 2009b).</i>
<b>Active substance</b>	<i>In plant protection products, active substances (also called ingredients) are responsible for specifically combating plant pests and/or plant diseases.</i>
<b>Acute Reference Dose</b>	<i>The Acute Reference Dose (ARfD) is an estimate of the amount of a substance in food or drinking water, expressed on a body weight basis, that can be ingested in a period of 24h or less without appreciable health risk to the consumer. It is expressed in milligrams of the chemical per kilogram of body weight (WHO/IPCS, 2009b).</i>
<b>Additive effect</b>	<i>The effects from individual chemicals, acting jointly in the mixture in a non-interactive manner, add up (i.e. 1+1+1=3).</i>
<b>Adverse effect</b>	<i>Change in the morphology, physiology, growth, reproduction, development or lifespan of an organism which results in impairment of functional capacity to compensate for additional stress or increased susceptibility to the harmful effects of other environmental influences (JRC, 2014).</i>
<b>Aggregate exposure</b>	<i>Refers to the exposure to a single chemical from multiple sources and by multiple pathways and routes. Used in general as a synonym of 'combined exposure'.</i>
<b>Antagonistic effect</b>	<i>The individual chemicals in the mixture reduce or cancel out each other's effect(s), resulting in combined effects smaller than the sum of the individual effects (referred to as 'less-than-additive') (i.e. 1+1+1&lt;3).</i>
<b>Benchmark Dose</b>	<i>The Benchmark Dose (BMD) is a dose level, derived from the estimated dose-response curve, associated with a specified change in response, i.e. a BMD10 corresponds to a 10% change in response, e.g. the increase in incidence of cancer.</i>
<b>Co-formulant</b>	<i>Co-formulants (or 'inert ingredients') are mixed together with active substances in order to influence the properties of a plant protection product. Co-formulants do not exhibit pesticidal activity but may still be biologically or chemically active</i>
<b>Coincidental mixtures</b>	<i>Complex mixtures of unknown/varying composition of unrelated chemicals co-occurring in environmental media (water, soil, air), biota, feed, food, or human tissues as a result of releases from various sources and through multiple routes of exposure.</i>
<b>Combined exposure</b>	<i>Refers to the exposure to a single chemical from multiple sources and by multiple pathways and routes. Used in general as a synonym of 'aggregate exposure'.</i>
<b>Common Mechanism Groups</b>	<i>Common Mechanism Groups (CMGs) represent group of chemicals determined to cause a common toxic effect by a common mechanism of toxicity.</i>
<b>Component-based approach</b>	<i>An approach in which the risk of a mixture is assessed based on exposure and effect data of its individual components (EFSA, 2018c).</i>
<b>Cumulative Assessment Groups</b>	<i>Cumulative Assessment Groups (CAGs) represent groups of active substances for which effects are assumed to be additive, based on the idea that pesticides causing similar toxic effects at different levels of biological organization can produce joint, cumulative toxicity even if they do not have similar mode of action.</i>
<b>Cumulative exposure</b>	<i>Describes the combined exposure to multiple chemicals by a single route, or the combined exposure to multiple chemicals by multiple routes.</i>
<b>Cumulative risk</b>	<i>For pesticides, cumulative risk has been defined by EFSA (2013c) as the risk resulting from exposure to more than one active substance via the diet (JRC, 2014).</i>

<b>Endocrine disruptor</b>	An exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations (WHO/IPCS, 2002).
<b>Good Agricultural Practice</b>	Good Agricultural Practice (GAP) in the use of pesticide includes the nationally authorized safe uses of pesticides under actual conditions necessary for effective and reliable pest control. It encompasses a range of levels of pesticide applications up to the highest authorised use, applied in a manner which leaves a residue which is the smallest amount practicable (WHO, 1997).
<b>Hazard</b>	A biological, chemical (e.g. a pesticide), or physical agent in, or condition of, food with the potential to cause harm (WHO, 1997) (see also adverse effect).
<b>Hazard Index</b>	The Hazard Index (HI) is the sum of the hazard quotients (HQ), i.e. the ratio between exposure and the reference value for the common toxic effect of each component in a mixture or a Common Assessment Group (JRC, 2014).
<b>Intended mixtures</b>	Intentionally manufactured mixtures of known composition that are regulated and placed on the market as chemical products or plant protection products.
<b>Maximum Cumulative Ratio</b>	The Maximum Cumulative Ratio (MCR) is the ratio between the toxicity of the mixture (based on dose addition models) and the toxicity of the most contributing chemical in the mixture (Kienzler et al., 2016).
<b>Limit of Determination</b>	The lowest limit of analytical determination (LOD) is the lowest concentration of a pesticide residue or contaminant that can be identified and quantitatively measured in a specified food, agricultural commodity, or animal feed with an acceptable degree of certainty by a regulatory method of analysis (WHO, 1997).
<b>Maximum Residue Level</b>	The maximum residue level (MRL) is the highest concentration of a pesticide residue that is legally tolerated to remain in or on a given food commodity and animal feed. It is defined for a single active ingredient and its relevant degradation products residues in/on a specific crop.
<b>Mixture</b>	A chemical mixture is the 'mix or solution of two or more substances' (as defined e.g. in the EU REACH and CLP Regulations). Any combination of two or more chemicals that may jointly contribute to real or potential effects regardless of source and spatial or temporal proximity. (EFSA, 2018c).
<b>Mode of action</b>	The concept of mode of action (MoA) describes the sequence of key biological events leading to an adverse effect in an organism, starting from the initiating event at the molecular level down to the cellular, organ and individual level.
<b>No-Observed Adverse Effect Level</b>	The NOAEL is the highest administered or calculated dose of a substance that does not result in a statistically or biologically significant increase in frequency or severity of an (adverse) effect. It is usually expressed in milligrams per kilogram of body weight per day.
<b>Plant protection product</b>	A plant protection product is the formulation of active substance and co-formulants.
<b>Pesticide</b>	Pesticides aim to prevent, control or kill a harmful organism ('pest') or a disease, or to protect plants or plant products during production, storage and transport. The term 'pesticide' includes plant protection products used for agricultural purposes, and biocide products used for non-agricultural purposes.
<b>Pesticide residue</b>	A pesticide residue is any specified substance in food, agricultural commodities, or animal feed resulting from the use of a pesticide. The term includes any derivatives of a pesticide, such as conversion products, metabolites, reaction products, and impurities that are considered to be of toxicological significance (WHO, 1997).
<b>Read-across</b>	Read-across is a method for predicting chemical-specific information (e.g. related to a test, such as a toxicological endpoint) for one substance by using similar chemical-specific information from (an)other substance(s). Applied to the context of mixture toxicity, read-

across can be used for unidentified or partially identified components in complex mixtures, for which the hazard evaluation is based on toxicity data for a sufficiently similar mixture.

**Reference point index**

The Reference point index (RfPI) represents the sum of exposures to each chemical component expressed as a fraction of their respective reference points (or points of departure) for the relevant effect (e.g. a NOAEL), in relation to their relative potencies (EC, 2012a).

**Risk assessment**

A scientifically based process which consists in four major steps: hazard identification, hazard characterization, exposure assessment, and risk characterization (WHO, 1997). An initial additional step, problem formulation, is often considered as part of the risk assessment paradigm.

**Risk communication**

The interactive exchange of information and opinions concerning risks among risk assessors, risk managers, consumers and other interested parties (WHO, 1997).

**Risk management**

The process of weighing policy alternatives based on the outcome of the risk assessment, which may involve if required, selecting and implementing appropriate control options, including regulatory measures (WHO, 1997).

**Synergistic effect**

The individual chemicals in the mixture reinforce each other's effect, resulting in combined effects greater than the sum of the individual effects (referred to as 'supra-additive' or 'greater-than-additive') (i.e.  $1+1>3$ ).

**Threshold of Toxicological Concern**

The Threshold of Toxicological Concern (TTC) is a "read across" method for estimating of the maximum "safe" exposure threshold value for (groups of) chemicals below which there would be no appreciable risk to human health, whether chemical-specific toxicity data are available or not (Kroes et al., 2005).

**Toxic Equivalency Factor**

The Toxic Equivalency Factor (TEF) is the ratio of the toxicity of a chemical to that of another structurally related chemical (or index compound) chosen as a reference (JRC, 2014). The TEF is the scaling factor.

**Toxic Equivalent**

In the TEF method, the Toxic Equivalent (TEQ) equals the summation of the mixture components doses each multiplied by the respective TEF.

**Toxicodynamic interaction**

Describes the interaction of a toxicant (e.g. a component of a mixture) with a target site (typically a protein) and its biological effects. Such an interaction may result in the components of a mixture to compete for the same molecular and cellular processes.

**Toxicokinetic interaction**

Describes the interaction of a toxicant (e.g. a component of a mixture) with an organism at the level of absorption, distribution, metabolism, and excretion processes.

**Whole mixture approach**

A risk assessment approach in which the mixture is treated as a single entity, similar to single chemicals, and so requires dose-response information for the mixture of concern or a (sufficiently) similar mixture (EFSA, 2018c).