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Report on mixtures and implementation strategy in Europe –

**Assessment of chemical mixtures under consideration of current and future
regulatory requirements and scientific approaches.**

WP 9 – International harmonization and implementation

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APPENDIX - EUROMIX DELIVERABLE 9.1

*Report on mixtures and implementation strategy in Europe -
Assessment of chemical mixtures under consideration of current and
future regulatory requirements and scientific approaches.*

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Table A 1: Terms and definition in the context of cumulative exposure and cumulative risk assessment with regard to human risk assessment based on (Groß et al., 2011), extended by definitions given by EFSA as well as legal directives and regulations in the field of chemical substances and products.

Term	Definition	Reference	Remarks
Acceptable daily intake	‘acceptable daily intake’ means the estimate of the amount of substances in food expressed on a body weight basis, that can be ingested daily over a lifetime, without appreciable risk to any consumer on the basis of all known facts at the time of evaluation, taking into account sensitive groups within the population (e.g. children and the unborn).	Regulation EC No. 396/2005	
Active substance	‘active substance’ means a substance or a micro-organism that has an action on or against harmful organisms;	Regulation EU No. 528/2012	
	Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.	Directive 2001/83/EC	
Acute reference dose	‘acute reference dose’ means the estimate of the amount of substance in food, expressed on a body weight basis, that can be ingested over a short period of time, usually during one day, without appreciable risk to the consumer on the basis of the data produced by appropriate studies and taking into account sensitive groups within the population (e.g. children and the unborn);	Regulation EC No. 396/2005	
Additive effect	Consequence that follows exposure to two or more physicochemical agents which act jointly but do not interact. The total effect is the simple sum of the effects of separate exposure to the agents under the same conditions (IUPAC 2006; cited from BfR 2009)	Groß, et al. 2011	EFSA 2008 refers to the IUPAC definition
Adverse Outcome Pathway (AOP)	An Adverse Outcome Pathway (AOP) is a conceptual construct that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment.	Ankley <i>et al.</i> , 2009	In practice the AOP links the initial chemical interaction known as the molecular initiating event (MIE) to progressive levels of biochemical organisation at the individual or population level.
	The sequence of major biochemical events following the initial chemical interaction that are required to elicit the toxic effect constitute the Adverse	US EPA, 2016	

Term	Definition	Reference	Remarks
	Outcome Pathway (AOP).		
Adverse reaction	A reaction to a veterinary medicinal product which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or to restore, correct or modify a physiological function.	Directive 2001/82/EC	
	A response to a medicinal product which is noxious and unintended.	Directive 2001/83/EC	
Aggregate exposure	Exposure to the same substance by multiple pathways and routes is likely best described as “Single Chemical, All Routes” (referenced in some jurisdictions as “Aggregate Exposure”).	WHO/IPCS 2009	
	Sum total of all exposure to pesticides through inhalation, dermal, oral, or optic contact (IUPAC 2006; cited from BfR 2009)	Groß, et al. 2011	
	Exposure to one chemical from all sources, for example; total exposure for someone living near to an industrial site from food, air, water and soil (UK Food Standards Agency 2002)	Groß, et al. 2011	
	The demographic, spatial and temporal characteristics of exposure to a single chemical through all relevant pathways (e.g. food, water, residential uses, occupational) and routes (e.g. oral, dermal, inhalation) (WHO/IPCS 2009)	Groß, et al. 2011	
	“[...] “aggregate” and “cumulative” are used as adjectives to modify “exposure” or “dose” without further elaboration. Often, “aggregate” and “cumulative” seem to be used interchangeably, suggesting (1) exposures that are from multiple sources, received via multiple exposure pathways, or doses received through multiple routes; (2) exposures or doses that accumulate over time, often over a lifetime; or (3) exposures or doses from more than one chemical or stressor simultaneously or sequentially” (IPCS 2004)	Groß, et al. 2011	The Exposure Assessment Terminology Working Group [of the IPCS] identified four terms that were particularly difficult to define due to their relatively recent emergence as exposure terms. These are aggregate exposure, aggregate dose, cumulative exposure, and cumulative dose. In studying the literature, the Exposure Assessment Terminology Working Group found very few formal definitions of these terms (IPCS 2004)
	Aggregate exposure assessment combines exposure from different pathways such as food, air and water and is important in considering the total personal	Groß, et al. 2011	Focus on human health risk assessment; definition in connection with pesticides

Term	Definition	Reference	Remarks
	exposure to a given chemical (UK Food Standards Agency 2002)		
	'Aggregate exposure' refers to the combined exposures to a single chemical across multiple routes (oral, dermal, inhalation) and across multiple pathways (food, drinking water, residential)	US EPA, 2001a	
Aggregated risk	The risk associated with all pathways and routes of exposure to a single chemical (EFSA 2008 according to definition by US EPA 2002; cited from BfR 2009)	Groß, et al. 2011	
	Aggregate risk is the risk associated with multiple pathways / routes of exposure to a single chemical (WHO/IPCS 2009)	Groß, et al. 2011	
	'Aggregate Risk' is the likelihood of the occurrence of an adverse health effect resulting from all routes of exposure to a single substance.	US EPA, 2001a	
Aggregate risk assessment	Different routes of exposure to the same active substance, which considers: <ul style="list-style-type: none"> the use of the same active substance in different biocidal PTs (e.g. wood preservative and insecticide) the use of the same active substance under different regulations (e.g. biocides, pesticides, veterinary drugs) the exposures from food, drinking water, and residential / nonoccupational uses (US EPA 2002; cited from BfR 2009) 	Groß, et al. 2011	Focus on human health risk assessment
	Risk assessment taking all sources of intake of a given pesticide into account (UK Food Standards Agency 2002; cited from BfR 2009)	Groß, et al. 2011	UK Food Standards Agency restricts the definition to a given pesticide that might contain several active compounds.
Antagonism	Antagonism occurs when "the effect of the mixture is less than that estimated for additivity on the basis of the toxicities of the components.	EFSA, 2013a	
Bystander	Bystanders are people who casually are located within or directly adjacent to an area where application of a plant protection product is in process or has taken place, but not for the purpose of working on the treated area or with the treated commodity.	Regulation EU No. 284/2013	
Candidate common mechanism group	A 'candidate common mechanism group or candidate CMG' represents a group of pesticides for which toxicological information on chemical structure, apical endpoint, pesticidal MOA and/or mammalian mechanistic information suggest the potential for a common mechanism of toxicity but do not have	US EPA, 2016	

Term	Definition	Reference	Remarks
(candidate CMG)	adequate data for establishing key events in a pathway as described in the MOA/AOP framework (e.g., lack of dose or temporal concordance of proposed key events).		
Combined exposure	Combined exposure of humans via two or more routes (EU TGD 2003, Part I); Exposure to a substance under different circumstances (e.g. exposure at the workplace and exposure from consumer products / indirect exposure via the environment) (EU TGD 2003, Part III)	Groß, et al. 2011	The term “combined exposure” is used in the EU TGD solely within the scope of consumer exposure assessment.
Combination effect; mixture effect; joint effect	The response of a biological system to several chemicals, either after simultaneous or sequential exposure. The terms are used synonymously (Kortenkamp & Hass 2009)	Groß, et al. 2011	
Combined toxicity	Combined toxicity is defined as the “response of a biological system to several chemicals, either after simultaneous or sequential exposure and can take three possible forms: dose-addition, response-addition or interaction	EFSA, 2013a	
Common mechanism endpoint	A ‘common mechanism endpoint(s)’ is/are those common toxic effect(s) which are pertinent and sensitive endpoints associated with the common mechanism which will provide a scientifically sound basis for determining relative potency of chemicals in a cumulative risk assessment.	US EPA, 2016	
Common mechanism group (CMG)	A ‘common mechanism group or CMG’ is a group of chemicals that induce a common toxic effect by a common mechanism of toxicity	US EPA, 2002b	
Common mechanism of toxicity	‘Common mechanism of toxicity’ pertains to two or more pesticide chemicals or other substances that cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (i.e., interpreted as mode of action).	US EPA, 1999a, 2002a, 2016	
Common toxic effect	‘Common toxic effect’ is a toxic effect that occurs in or at the same anatomical or physiological site or locus (e.g. same organ or tissue).	US EPA, 1999a	There is a critical difference between a common and a cumulative toxic effect.
Concurrent Exposure	Interpreted as potential human exposure by all relevant pathways, durations, and routes that allow one chemical to add to the exposure of another chemical such that the total risk is an estimate of the sum of the exposures to the individual chemicals. This includes simultaneous exposures as well as any	Groß, et al. 2011	

Term	Definition	Reference	Remarks
	sequential exposures that could contribute to the same joint risk, either by overlapping internal doses or by overlapping toxic effects (US EPA 2002, EFSA 2008; cited from BfR 2009)		
Cumulative assessment groups (CAG)	A group of chemicals that could plausibly act by a common mode of action, not all of which will necessarily do so. Membership of a CAG can usually be refined (reduced) by application of successively higher tiers of the approach described in this Opinion (EFSA 2008; cited from BfR 2009)	Groß, et al. 2011	
	'Cumulative Assessment Group (CAG)' is a subset of chemicals selected from a common mechanism group for inclusion in a refined quantitative estimate of risk.	US EPA, 2002a	
Cumulative exposure	Exposure to multiple chemicals on the basis of whether they have a common mechanism of action (UK Food Standards 2002)	Groß, et al. 2011	
	Cumulative exposure defines the aggregate exposure to multiple chemicals (WHO/IPCS 2009)	Groß, et al. 2011	
	It is recommended that exposure to "multiple chemicals by a single route" be distinguished from exposure to "multiple chemicals by multiple routes" (referenced in some jurisdictions as "cumulative" exposure).	Meek et al., 2011	It is recommended to use the term "combined exposure to multiple chemicals" when referring to both exposure to multiple chemicals by a single route and exposure to multiple chemicals by multiple routes.
	Cumulative exposure: "combined exposure to multiple chemicals including all routes, pathways, and sources of exposure to multiple chemicals"	EFSA, 2013a	
Cumulative exposure assessment	Cumulative [exposure] assessment estimates exposure to multiple chemicals on the basis of whether they have a common mechanism of action (WHO/IPCS 2009)	Groß, et al. 2011	
	An assessment that describes concurrent spatial and temporal characteristics of exposure performed for a set of chemicals (ILSI 1999; cited from BfR 2009)	Groß, et al. 2011	
Cumulative risk	Probability of any defined harmful effect occurring through a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals that share a common mechanism of toxicity (IUPAC 2006; cited from BfR 2009)	Groß, et al. 2011	

Term	Definition	Reference	Remarks
	Cumulative risk is the combined risk from aggregate exposure to multiple chemicals (and may be restricted to chemicals that have a common mechanism of toxicity) (WHO/IPCS 2009)	Groß, et al. 2011	
	Cumulative risk: “the combined risks from aggregate exposures to multiple agents or stressors” which may include chemicals, as well as biological or physical agents.	EFSA, 2013a	
	Cumulative Risk is the risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals that share a common mechanism of toxicity.	US EPA, 2002a	
	Taking intake of more than one pesticide into account (UK Food Standards Agency 2002; cited from BfR 2009)	Groß, et al. 2011	
	Exposure to multiple substances by multiple pathways (including food, drinking water, and residential / nonoccupational exposure to air, soil, grass, and indoor surfaces) (US EPA 2002; cited from BfR 2009)	Groß, et al. 2011	
Cumulative risk assessment	An assessment that describes concurrent spatial and temporal characteristics of exposure performed for a set of chemicals (ILSI 1999; cited from BfR 2009)	Groß, et al. 2011	EFSA 2008 also refers to the IUPAC definition, with an additional note: “in the context of this opinion, it is intended more specifically to be the risk deriving from the exposure to compounds that share the same mode of action (dose addition) or that have similar effects but do not act at the same molecular target (response addition) and is contrasted to synergistic risk. Although the term “cumulative risk” has sometimes been used when referring generally to the risk from exposure to more than one pesticide (see EFSA colloquium), in the context of this opinion, it refers more specifically to the risk deriving from combined exposure to compounds that share the same mode of action or that have similar effects but by

Term	Definition	Reference	Remarks
			different modes of action (EFSA 2008; cited from BfR 2009)
	Risk assessment approaches that consider the impact of multiple chemical exposures, from multiple sources, routes and pathways, over multiple time frames (Kortenkamp & Hass 2009)	Groß, et al. 2011	Cumulative risk assessment (CRA), mixtures risk assessment: The terms are used synonymously by Kortenkamp & Hass (2009) "It is worth noting that the European use of the term "cumulative risk assessment" encompasses multiple sources, routes and pathways, but restricts considerations to one chemical, not multiple chemicals. For the purposes of this report, the European use of the term is ignored." (Kortenkamp & Hass 2009)
Cumulative toxic effect	The 'cumulative toxic effect' is the net change in magnitude of a common toxic effect resulting from exposure to at least two chemicals causing the same toxic effect by a common mechanism.	US EPA, 1999a	There is a critical difference between a common and a cumulative toxic effect (see definition of common toxic effect)
Dose Additivity	When the effect of the combination is the effect expected from the equivalent dose of an index chemical. The equivalent dose is the sum of component doses scaled by their potency relative to the index chemical.	US EPA, 2003	Dose addition assumes by definition that chemicals in a mixture are non-interactive and elicit a common response through similar actions on a biological system, acting as concentrations or dilutions of each other.
Effect assessment	Combination of analysis and inference of possible consequences of the exposure to a particular agent (e.g., pesticide) based on knowledge of the dose-effect relationship associated with that agent in a specific target organism, system, or (sub-) population (IUPAC 2006)	Groß, et al. 2011	
	The effects assessment comprises the following steps of the risk assessment procedure: 1) hazard identification: The aim of the hazard identification is to identify the effects of concern; 2) dose (concentration) – response (effect) assessment: At this step the predicted no effect concentration (PNEC), shall, where possible, be determined. (EU TGD 2003).	Groß, et al. 2011	
Exposure	Contact between an agent and a target. Contact takes place at an exposure	Groß, et al.	

Term	Definition	Reference	Remarks
	surface over an exposure period (ISEA glossary 2005; cited from BfR 2009)	2011	
	Concentration or amount of a pesticide (or agent) that reaches a target organism, system, or (sub-) population in a specific frequency for a defined duration (IUPAC 2006; cited from BfR 2009)	Groß, et al. 2011	EFSA 2008 refers to IUPAC 2006
	Relates to the following options: simultaneous and/or sequential exposure, nature of exposure: duration, frequency, timing, magnitude of exposure: exposure concentration and dose (US EPA 2002; cited from BfR 2009)	Groß, et al. 2011	
	Exposure to the same substance by multiple pathways and routes is likely best described as “Single Chemical, All Routes” (referenced in some jurisdictions as “Aggregate Exposure”). Similarly, it is recommended that exposure to “Multiple Chemicals by a Single Route” be distinguished from “Multiple Chemicals by Multiple Routes”. To this end, the framework being developed addresses “Combined Exposures to Multiple Chemicals” (WHO/IPCS 2009)	Groß, et al. 2011	
	Exposure (of the environment) results from discharges and/or releases of chemicals. (EU TGD 2003)	Groß, et al. 2011	
Exposure assessment	The process of estimating or measuring the magnitude, frequency and duration of exposure to an agent, along with the number and characteristics of the population exposed. Ideally, it describes the sources, pathways, routes, and the uncertainties in the assessment (ISEA glossary 2005; cited from BfR 2009)	Groß, et al. 2011	EFSA 2008 refers to ISEA glossary 2005
	Evaluation of the exposure of an organism, system, or (sub-) population to a pesticide or agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment (IUPAC 2006; cited from BfR 2009)	Groß, et al. 2011	
	The environment may be exposed to chemical substances during all stages of their life-cycle from production to disposal or recovery. For each environmental compartment (air, soil, water, sediment) potentially exposed, the exposure concentrations should be derived. (EU TGD 2003)	Groß, et al. 2011	
Exposure pathway	The course an agent takes from the source to the target (ISEA glossary 2005; cited from BfR 2009)	Groß, et al. 2011	EFSA 2008 refers to ISEA glossary 2005
	The physical course a substance takes from the source to the organism exposed (e.g., through food or drinking water consumption or residential	Groß, et al. 2011	

Term	Definition	Reference	Remarks
	substance / biocidal uses). (US EPA 2002; cited from BfR 2009)		
	The physical course a chemical or pollutant takes from the source to the organism exposed. Also called exposure pathway.	US EPA, 1992	Cited in US EPA, 2001a
Exposure route	The way an agent enters a target after contact (e.g., by ingestion, inhalation, or dermal absorption) (ISEA glossary 2005; cited from BfR 2009)	Groß, et al. 2011	EFSA 2008 refers to ISEA glossary 2005; US EPA very similar definition
	The way a chemical or pollutant enters an organism after contact, e.g., by ingestion, inhalation, or dermal absorption.	US EPA, 1992	Cited in US EPA, 2001a
Exposure scenario	Exposure scenario: means the set of conditions, including operational conditions and risk management measures, that describe how the substance is manufactured or used during its life-cycle and how the manufacturer or importer controls, or recommends downstream users to control, exposures of humans and the environment. These exposure scenarios may cover one specific process or use or several processes or uses as appropriate;	Regulation EC No. 1907/2006	
	A combination of facts, assumptions, and inferences that define a discrete situation where potential exposures may occur. These may include the source, the exposed population, the time frame of exposure, microenvironment(s), and activities. Scenarios are often created to aid exposure assessors in estimating exposure (ISEA glossary 2005; cited from BfR 2009)	Groß, et al. 2011	EFSA 2008 refers to ISEA glossary 2005; US EPA very similar definition
	Generic exposure scenarios assume that substances are emitted into a non-existing model environment with predefined agreed environmental characteristics. These environmental characteristics can be average values or reasonable worst-case values depending on the parameter in question. Generic exposure scenarios have been defined for local emissions from a point source and for emissions into a larger region. When more specific information on the emission of a substance is available, it may well be possible to refine the generic or site-specific assessment. (EU TGD 2003)	Groß, et al. 2011	
Group of similar mixtures	A 'group of similar mixtures' refers to chemically related classes of mixtures that act by a similar mode of action, have closely related chemical structures, and occur together routinely in environmental samples, usually because they are generated by the same commercial process.	US EPA, 2000	

Term	Definition	Reference	Remarks
Hazard class	'hazard class' means the nature of the physical, health or environmental hazard;	Regulation EU No. 1272/2008	
Hazard category	'hazard category' means the division of criteria within each hazard class, specifying hazard severity;	Regulation EU No. 1272/2008	
Hazard Quotient (HQ)	A 'hazard quotient (HQ)' is estimated as the ratio of the estimated exposure to the reference value (e.g. Tolerable Daily Intake (TDI), Tolerable Air Concentration).	Health Canada, 2010a,b	
Hazard Index (HI)	The 'Hazard Index (HI)' is defined as a weighed sum of the exposure measures for the mixture component chemicals.	US EPA, 2000	The "weight" factor according to dose addition should be a measure of the relative toxic strength, sometimes called potency.
Impurity	'impurity' means any component other than the pure active substance and/or variant which is present in the technical material (including components originating from the manufacturing process or from degradation during storage).	Regulation EU No. 1107/2009	
Index chemical	The 'index chemical' is a chemical from the CAG used as a point of reference for standardising the common toxicity of the other chemical members of the CAG.	US EPA, 2002a	The index chemical is not necessarily the most potent chemical in the CAG, but rather one that is well-defined toxicologically and has a high quality database.
Interaction	Interactions occur "when the effect of a mixture differs from additivity based on the dose-response relationships of the individual components". Interactions refer to joint action between multiple chemicals that differ from dose addition or response addition and are categorised as less than additive (antagonism, inhibition, masking) or greater than additive (synergism, potentiation).	EFSA, 2013a	
Margin of Exposure	The margin of exposure (MOE) is a numerical value providing a measure of how close is the exposure to the point of departure. It is the ratio of the point of departure (usually a NOAEL) divided by the anticipated or actual measure of human exposure.	US EPA, 2002a, 2002b	
Maximum residue level (MRL)	'maximum residue level' (MRL) means the upper legal level of a concentration for a pesticide residue in or on food or feed set in accordance with this Regulation, based on good agricultural practice and the lowest consumer	Regulation EC No. 396/2005	

Term	Definition	Reference	Remarks
	exposure necessary to protect vulnerable consumers;		
	'maximum residue limit' means the maximum concentration of residue resulting from the use of an additive in animal nutrition which may be accepted by the Community as being legally permitted or recognised as acceptable in or on a food;	Regulation EC No. 1831/2003	
Mechanism of action	"Mechanism of Action (MEA)" refers to "a detailed explanation of the individual biochemical and physiological events leading to a toxic effect" (Boobis et al., 2006; EFSA, 2008a, 2013).	EFSA, 2013a	
Mechanism of toxicity	'Mechanism of toxicity' is defined as the major steps leading to a toxic effect following interaction of a pesticide with biological targets.	US EPA, 2016	As cited in US EPA, 2016, this definition of mechanism of toxicity is similar to the concept of mode of action (MOA) as defined by EPA's Cancer Guidelines (USEPA, 2005) and other international efforts through OECD and WHO (Boobis <i>et al.</i> , 2008; Seed <i>et al.</i> , 2005; Sonich-Mullin <i>et al.</i> , 2001; Meek <i>et al.</i> , 2014).
Mixture	'mixture' means a mixture or solution composed of two or more substances;	Regulation EU No. 1272/2008 Regulation EU No. 1223/2009	Regulation EU No. 528/2012 refers to 1907/2006
	A "mixture" has been defined as "any combination of two or more chemicals, regardless of source and spatial or temporal proximity that may jointly contribute to actual or potential effects in a receptor population."	EFSA, 2013a	
	'Mixtures' are defined as any combination of two or more chemical substances regardless of source or of spatial or temporal proximity.	US EPA, 2000	According to this definition of the mixtures presented in the US EPA guidelines for the health risk assessment of environmental pollutants, the mixtures may include compounds generated simultaneously from a single source of process (e.g. coke oven emissions and diesel exhaust) or produced as commercial products eventually released

Term	Definition	Reference	Remarks
			to the environment (e.g. PCBs, gasoline and pesticide formulations), or even placed in the same area for disposal or storage, eventually coming into contact with each other and released as a mixture in the environment.
Mixture risk assessment	In the following, the term “mixture assessment” is used for the risk assessment of mixtures. It consists of hazard assessment, exposure assessment and risk characterisation.	Bunke et al., 2014	
Mixture toxicity/ mixture effect/ joint effect	“Mixture toxicity”, refers to the hazard assessment of mixtures only. It is a synonym to “mixture effects”.	Bunke et al., 2014	
	“Mixture effect”, “joint effect” and “mixture toxicity” are used synonymously and refer to the biological response and thus to the potential adverse effects caused by mixtures after simultaneous or sequential exposure. Mixture may be hazardous due to interactions or due to additivity of the chemical components.	Rotter et al., 2016. Deliverable 9.1	
Mode of action	A postulated mode of action is a biologically plausible sequence of key events leading to an observed effect supported by robust experimental Observations and mechanistic data. It describes key cytological and biochemical events—that is, those that are both measurable and necessary to the observed effect. Mode of action contrasts with “Mechanism of Action”, which generally involves a sufficient understanding of the molecular basis for an effect so that causation can be established (Sonich Mullin et al., 2001).	WHO/IPCS, 2009	
	“Mode of Action (MOA)” refers to the “biologically plausible sequence of key events leading to an observed effect supported by robust experimental observations and mechanistic data. It refers to the major steps leading to an adverse health effect following interaction of the compound with biological targets; it does not imply full understanding of mechanism of action at the molecular level.	EFSA, 2013a	
	The term ‘Mode of Action’ is defined as a series of key events and processes starting with interaction of an agent with a cell, and proceeding through	US EPA, 2000	

Term	Definition	Reference	Remarks
	operational and anatomical changes causing disease formation.		
Operator	Operators are people who are involved in activities relating to the application of a plant protection product, such as mixing, loading, application, or relating to cleaning and maintenance of equipment containing a plant protection product; operators may be professionals or amateurs.	Regulation EU No. 284/2013	
Overall exposure	Caused by the substance shall be reviewed by integrating the results for the overall releases, emissions and losses from all sources to all environmental compartments (Regulation (EC) No 1907/2006, Annex 1)	Groß, et al. 2011	
Pesticide	The term 'pesticide' is defined as (1) any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, (2) any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant, and (3) any nitrogen stabilizer, except that the term "pesticide" shall not include any article that is a "new animal drug" [...], or that is an animal feed [...] bearing or containing a new animal drug.	FIFRA, 2012	
Pesticide residues	'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 as defined in Article 2, point 1 of Directive 91/414/EEC, which are present in or on the products covered by Annex I to this Regulation, including in particular those which may arise as a result of use in plant protection, in veterinary medicine and as a biocide;	Regulation EC No. 396/2005	
Point of Departure (POD)	A point of departure (POD) is a dose that can be considered to be in the range of observed responses, without significant extrapolation. A POD can be a data point or an estimated point that is derived from observed dose-response data.	US EPA, 2002b	A POD is used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures.
Preparation	Preparation: means a mixture or solution composed of two or more substances;	Regulation EC No. 1907/2006	
	'preparations' means mixtures or solutions composed of two or more substances intended for use as a plant protection product or as an adjuvant;	Regulation EU No. 1107/2009	
Relative Potency Factor (RPF)	'Relative Potency Factor (RPF)' is a ratio of the toxic potency of a given chemical to that of an index chemical in the CAG.	US EPA, 2002a	The index chemical is a chemical from the CAG used as a point of reference for standardising the common toxicity of the

Term	Definition	Reference	Remarks
			other chemical members of the CAG. Relative potency factors are used to convert exposures of all chemicals in the CAG into their exposure equivalents of the index chemical.
Residents	Residents are people who live, work or attend any institution near to areas that are treated with plant protection products, but not for the purpose of working on the treated area or with the treated commodity.	Regulation EU No. 284/2013	
Residue	'residue' means a substance present in or on products of plant or animal origin, water resources, drinking water, food, feed or elsewhere in the environment and resulting from the use of a biocidal product, including such a substance's metabolites, breakdown or reaction products;	Regulation EU No. 528/2012	
	'residues' means one or more substances present in or on plants or plant products, edible animal products, drinking water or elsewhere in the environment and resulting from the use of a plant protection product, including their metabolites, breakdown or reaction products;	Regulation EU No. 1107/2009	
Response addition	Response addition is the default approach when the component chemicals are functionally independent. Under 'response addition', the general procedure is to first determine the risks per the exposure for the individual components; the mixture risk is then estimated by adding the individual risks together.	US EPA, 2000	Response addition assumes that the components of the mixture are functionally independent of one another at low exposure levels. Response addition is different from dose addition in that it does not assume similar kinetics or a similar mode of action and does not assume that the dose-response curves have similar shape.
Similar Mode of Action	For the evaluation of chemical mixtures in case of environmental pollutants, a 'similar mode of action' across mixtures or mixture components may require that these chemicals act only on the same target organ.	US EPA, 2000	
Source	The origin of an agent for the purposes of an exposure assessment (ISEA glossary 2005)	Groß et al., 2011	
Substance	Substance: means a chemical element and its compounds in the natural state	Regulation EC	Regulation EU No. 528/2012 refers to

Term	Definition	Reference	Remarks
	or obtained by any manufacturing process, including any additive necessary to preserve its stability and any impurity deriving from the process used, but excluding any solvent which may be separated without affecting the stability of the substance or changing its composition;	No. 1907/2006; Regulation EU No. 1272/2008; Regulation EU No. 1223/2009	Regulation EC 1907/2006
	‘substances’ means chemical elements and their compounds, as they occur naturally or by manufacture, including any impurity inevitably resulting from the manufacturing process;	Regulation No. EU 1107/2009	
	Substance: Any matter irrespective of origin which may be: <ul style="list-style-type: none"> • human, e.g. human blood and human blood products; • animal, e.g. micro-organisms, whole animals, parts of organs, animal secretions, toxins, extracts, blood products; • vegetable, e.g. micro-organisms, plants, parts of plants, vegetable secretions, extracts; • chemical, e.g. elements, naturally occurring chemical materials and chemical products obtained by chemical change or synthesis. 	Directive 2001/82/EC; Directive 2001/83/EC	
	The term ‘substance’ is defined by CEPA as any distinguishable kind of organic or inorganic matter, whether animate or inanimate, and includes [...] any mixture that is a combination of substances [...], and any complex mixtures of different molecules that are contained in effluents, emissions or wastes that result from any work, undertaking or activity.	CEPA, 1999	
Synergism	Synergism occurs when “the effect of the mixture is greater than that estimated for additivity on the basis of the toxicities of the components”.	EFSA, 2013a	
Tolerance	A pesticide tolerance is the maximum amount of a pesticide allowed to remain in or on a food, as part of the process of regulating pesticides.	FFDCA, 2016	The pesticide tolerance under the FFDCA definition is known in the EU as the MRL (see MRL definition).
Toxic effect	‘Toxic effect’ is an effect known (or can reasonably expected) to occur in humans, that results from exposure to a chemical substance and that will or can reasonably be expected to endanger or adversely affect quality of life, e.g.	US EPA, 1999a	The ‘toxic effect’ as defined by US EPA is known as ‘adverse effect’ under EU legislation.

Term	Definition	Reference	Remarks
	acute lethality, loss of hearing, renal tubule necrosis, cardiomyopathy etc		
Toxic substance	A substance is considered to be toxic if it is "...entering or may enter the environment in a quantity or concentration or under conditions that: a. have or may have an immediate or long-term harmful effect on the environment or its biological diversity; b. constitute or may constitute a danger to the environment on which life depends; or c. constitute or may constitute a danger in Canada to human life or health.	CEPA, 1999	
UFA	UFA is a ≤ 10 -fold UF intended to account for uncertainty in extrapolating data from laboratory animals to project human risk, considered to include toxicokinetic/dynamic processes.	US EPA, 2002b	
UFD_b	UFD _b is a ≤ 10 -fold factor is used to address database deficiencies, which are not addressed by UFL and UFS factors, in estimating the relative toxic potency of each chemical member of the CAG.	US EPA, 2002b	
UFD_b CAG	UFD _b CAG is a ≤ 10 -fold factor is used to address database deficiencies that are common to the CAG.	US EPA, 2002b	
UFH	UFH is a ≤ 10 -fold UF intended to account for potential variation in sensitivity among humans and is considered to include toxicokinetic/dynamic processes.	US EPA, 2002b	
UFL	UFL is a ≤ 10 -fold factor is used to estimate a NOAEL from a LOAEL for a specific chemical's relative toxic potency factor.	US EPA, 2002b	
UFS	UFS is a ≤ 10 -fold factor is used to estimate a chronic point of departure from a study of less than chronic treatment duration for a specific chemical's relative toxic potency factor.	US EPA, 2002b	
Use	Use: means any processing, formulation, consumption, storage, keeping, treatment, filling into containers, transfer from one container to another, mixing, production of an article or any other utilisation;	Regulation EC No. 1907/2006; Regulation EU No. 1272/2008	
	'use' means all operations carried out with a biocidal product, including storage, handling, mixing and application, except any such operation carried out with a view to exporting the biocidal product or the treated article outside	Regulation EU No. 528/2012	

Term	Definition	Reference	Remarks
	the Union;		
Vulnerable groups	'vulnerable groups' means persons needing specific consideration when assessing the acute and chronic health effects of biocidal products. These include pregnant and nursing women, the unborn, infants and children, the elderly and, when subject to high exposure to biocidal products over the long term, workers and residents;	Regulation EU No. 528/2012	
	'vulnerable groups' means persons needing specific consideration when assessing the acute and chronic health effects of plant protection products. These include pregnant and nursing women, the unborn, infants and children, the elderly and workers and residents subject to high pesticide exposure over the long term;	Regulation No. EU 1107/2009	
Worker	Workers are people who, as part of their employment, enter an area that has previously been treated with a plant protection product or who handle a crop that has been treated with a plant protection product.	Regulation EU No. 284/2013	

References

Ankley, G.T., Bennett, R.S., Erickson, R.J., Hoff, D.J., Hornung, M.W., Johnson, R.D., Mount, D.R., Nichols, J.W., Russom, C.L., Schmieder, P.K., Serrano, P.K., Tietge, J.E., Villeneuve, D.L., 2010. Adverse outcome pathways: a conceptual framework to support ecotoxicology research and risk assessment. *Environmental Toxicology and Chemistry*, 29 (3), 730–741.

Bunke, D., Groß, R., Kalberlah, F., Oltmanns, J., Schwarz, M., Reihlein, A., Reineke, N., 2014. Mixtures in the Environment – Development of Assessment Strategies for the Regulation of Chemicals under REACH. Umweltbundesamt, Texte 65/2014. Available online: <https://www.umweltbundesamt.de/en/publikationen/mixtures-in-the-environment-development-of>

CEPA, 1999. Canadian Environmental Protection Act. Available online: <http://laws-lois.justice.gc.ca/eng/acts/c-15.31/>

Directive 2001/82/EC. Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products. *Official Journal of the European Communities*, L311, pp. 1-102.

Directive 2001/83/EC. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. *Official Journal of the European Communities*, L311, pp. 1-176.

EFSA (2013a). European Food Safety Authority. Scientific report of EFSA - International Frameworks Dealing with human risk assessment of combined exposure to multiple chemicals. *EFSA Journal* 2013, 11(7):3313.

FFDCA, 2012. Federal Food, Drug, and Cosmetic Act (FFDCA), United States Code, Title 21, 2016. Available online: <http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdca/>.

FIFRA, 2012. Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), as amended through P.L. 112–177, Effective September. 28, 2012. Available online: <http://www.agriculture.senate.gov/imo/media/doc/FIFRA.pdf>.

Groß, R., Bunke, D., Gartiser, S., 2011. Basic principles for the development of a concept for environmental exposure assessments of single substances released from multiple uses under REACH. Umweltbundesamt, TEXTE 63/2011. Available online: <https://www.umweltbundesamt.de/publikationen/basic-principles-for-development-of-a-concept-for>

- (EFSA, 2008) European Food Safety Authority – EFSA (Ed.); Opinion of the Scientific Panel on Plant Protection products and their Residues to evaluate the suitability of existing methodologies and, if appropriate, the identification of new approaches to assess cumulative and synergistic risks from pesticides to human health with a view to set MRLs for those pesticides in the frame of Regulation (EC) 396/2005; *The EFSA Journal* 704, 2008, 1-84
- (EU TGD, 2003) European Commission (Ed.); Technical Guidance Document in Support of Directive 93/67/EEC on Risk Assessment of New Notified Substances and Regulation (EC) No. 1488/94 on Risk Assessment of Existing Substances (Parts I, II, III and IV); Luxembourg, Office for the Official Publications of the European Community, 2003
- (UK Food Standards Agency, 2002) UK Food Standards Agency (Ed.), Committee on Toxicity of chemicals in Food, Consumer Products and the Environment; Risk Assessment of Mixtures of Pesticides and Similar Substances; September 2002
- (ILSI, 1999) Miles, B.; Faustman, E.; Olin, S.; Ryan, P.B.; Ferenc, S.; Burke, T., 1999. A Framework for cumulative risk assessment. An ILSI Risk Science Institute workshop report; International Life Sciences Institute; Washington.

- (IPCS, 2004) World Health Organization (Ed.); International Program on Chemical Safety – IPCS – Harmonization Project Document No. 1, IPCS Risk Assessment Terminology; Part 1: IPCS/OECD Key Generic Terms used in Chemical Hazard/Risk Assessment; Part 2: IPCS Glossary of Key Exposure Assessment Terminology; Geneva 2004
- (ISEA glossary, 2005) Zartarian, V.; Bahadori, T.; McKone, T., 2005. Adoption of an official ISEA glossary; Journal of exposure Analysis and Environmental Epidemiology, 15, 1-5
- (IUPAC, 2006) Stephenson, G.R.; Ferris, I.G.; Holland, P.T.; Nordberg, M., 2006. Glossary of Terms Relating to Pesticides (IUPAC Recommendations 2006). Pure and Applied Chemistry, 78(11), 2075–2154.
- (Kortenkamp and Hass, 2009) Kortenkamp, A.; Hass, U.; Expert workshop on combination effects of chemicals, 28-30 January 2009, Hornbæk, Denmark. Workshop Report organized under the auspices of the Danish Ministry of the Environment and the Danish Environmental Protection Agency; June 2009; http://www.mim.dk/NR/rdonlyres/C59693B7-2421-4748-89F0-5937496E0A28/0/BILAG_2_Expertworkshop.pdf
- (US EPA, 2002) U.S. Environmental Protection Agency (Ed.); Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity; Office of Pesticide Programs, U.S. Environmental Protection Agency Washington, D.C.; January 14, 2002; http://www.epa.gov/pesticides/trac/science/cumulative_guidance.pdf
- (WHO/IPCS, 2009) World Health Organisation – WHO (Ed.); Assessment of combined exposures to multiple chemicals: Report of a WHO/IPCS international workshop on aggregate/cumulative risk assessment; IPCS harmonization project document no. 7; 2009

Health Canada, 2010a. The federal contaminated site risk assessment in Canada, Part I: Guidance on human health preliminary quantitative risk assessment (PQRA). Version 2.0. Available online: http://www.hc-sc.gc.ca/ewh-semt/pubs/contamsite/part-partie_i/index-eng.php.

Health Canada, 2010b. The federal contaminated site risk assessment in Canada, Part V: Guidance on human health detailed quantitative risk assessment for chemicals (DQRACHEM). Available online: <http://www.hc-sc.gc.ca/ewh-semt/pubs/contamsite/chem-chim/index-eng.php>.

Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. Official Journal of the European Union, 24 November 2009, L309/1.

Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. Official Journal of the European Union, 22 December 2009, L342/59.

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. Official Journal of the European Union, 31 December 2008, L353/1.

Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. Official Journal of the European Union, 18 October 2003, L268/29.

Regulation (EC) No 1907/2006 of the European Parliament and the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/105/EC and 2000/21/EC. Official Journal of the European Union, 31 December 2006, L396/1.

Regulation (EU) No 284/2013 of 1 March 2013 setting out the data requirements for plant protection products, in accordance with Regulation (EC) No 1107/2009 of the European Parliament and of the Council concerning the placing of plant protection products on the market. Official Journal of the European Union, 1 March 2013, L93/85.

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. Official Journal of the European Union, 16 March 2005, L70/1.

Regulation (EU) No 528/2012 of the European Parliament and of the Council of 22 May 2012 concerning the making available on the market and use of biocidal products. Official Journal of the European Union, 27 June 2012, L167/1.

Rotter, S., Beronius, A., Hanberg, A., Zilliacus, J., Nikolopoulou, D., Machera, K., Solecki, R., 2016. Deliverable 9.1 - Report on mixtures and implementation strategy in Europe - Assessment of chemical mixtures under consideration of current and future regulatory requirements and scientific approaches. 1st version, October 28th, 2016. EuroMix - European Test and Risk Assessment Strategies for Mixtures, Project number 633172, Collaborative project: H2020-SFS-2014-2.

US EPA, 1999a. Guidance for Identifying Pesticide Chemicals and Other Substances That Have A Common Mechanism of Toxicity. Federal Register 64:5796-5799. Available online: <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-identifying-pesticide-chemicals-and-other>.

US EPA, 2000. US Environmental Protection Agency. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. Available online: <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20533>.

US EPA, 2001a. US Environmental Protection Agency. General principles for performing aggregate exposure and risk assessments. Environmental Protection Agency Office of Pesticide Programs, November 28, 2001. Available online: <https://www.epa.gov/sites/production/files/2015-07/documents/aggregate.pdf>.

- (US EPA, 1992) Guidance for Exposure Assessment. 57 FR 22888

US EPA, 2002a. US Environmental Protection Agency. A review of the reference dose and reference concentration processes. Risk Assessment Forum, US EPA, December 2002, EPA/630/P-02/002F. Available online: <http://www.epa.gov/raf/publications/pdfs/rfd-final.pdf>.

US EPA, 2002b. US Environmental Protection Agency. Guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity. Office of Pesticide Programs, January 14, 2002. Available online: https://www.epa.gov/sites/production/files/2015-07/documents/guidance_on_common_mechanism.pdf.

US EPA, 2003a. US Environmental Protection Agency. Developing relative potency factors for pesticide mixtures: Biostatistical analyses of joint dose-response. National Center for Environmental Assessment, Office of Research and Development, September, 2003 EPA/600/R-03/052. Available online: <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=66273&CFID=67106937&CFTOKEN=32784994>.

US EPA, 2016. US Environmental Protection Agency. Pesticide Cumulative Risk Assessment: Framework for Screening analysis purpose. Office of Pesticide Programs Office of Chemical Safety and Pollution Prevention, April 12, 2016. Available: <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework>.

- (US EPA, 2005) US Environmental Protection Agency. Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001F. Federal Register 70(66):17765–17817. Available online: <http://www.epa.gov/raf>
- Boobis, AR; Doe, JE; Heinrich-Hirsch, B; et al. (2008) IPCS framework for analyzing the relevance of a noncancer mode of action for humans. Critical Reviews in Toxicology, 38, 87–96.

- Seed, J; Carney, EW; Corley, RA; et al. 2005. Overview: using mode of action and life stage information to evaluate the human relevance of animal toxicity data. *Crit Rev Toxicol* 35(8-9):664-672.
- Sonich-Mullin, C; Fielder, R; Wiltse, J; et al. 2001. IPCS conceptual framework for evaluating a mode of action for chemical carcinogenesis. *Regul Toxicol Pharmacol*, 34, 146-152.
- Meek ME, Boobis A, Cote I, Dellarco V, Fotakis G, Munn S, Seed J, Vickers C. 2014. New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis. *Journal of Applied Toxicology*, 34(1), 1-18.

Meek, M.E., Boobis, A.R., Crofton, K.M., Heinemeyer, G., Raaij, M.V., Vickers, C., 2011. Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. *Regulatory Toxicology and Pharmacology*, 60, S1-S14.

WHO/IPCS, 2009. World Health Organization. Assessment of Combined Exposures to Multiple Chemicals: Report of a WHO/IPCS International Workshop on aggregated/cumulative risk assessment (Harmonization Project Document No. 7). World Health Organization, Geneva, Italy.