Brussels, 19 May 2025

COST 017/25

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action “Oxidative stress at the CrossroAds of adverse outcome Pathways -peSTicides - ONe hEalth” (CAPSTONE) CA24108

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action Oxidative stress at the CrossroAds of adverse outcome Pathways -peSTicides - ONe hEalth approved by the Committee of Senior Officials through written procedure on 19 May 2025.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA24108
OXIDATIVE STRESS AT THE CROSSROADS OF ADVERSE OUTCOME PATHWAYS -PESTICIDES - ONE HEALTH (CAPSTONE)

The COST Members through the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action, referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any document amending or replacing them.

The main aim and objective of the Action is to identify pesticides' adverse effects linked to oxidative stress (OxS) that are relevant for both humans and ecosystems, and to describe the Key Events (KE) involved in these effects. This will be achieved through the specific objectives detailed in the Technical Annex.

The present MoU enters into force on the date of the approval of the COST Action by the CSO.

OVERVIEW

Summary

Oxidative stress plays a central role in ecosystem disturbance and human pathologies. Some pesticides have already been banned due to their pro-oxidative properties which are linked to their adverse effects in both humans or in off-target organisms in ecosystem. However, several classes of pesticides are still authorized and could lead to oxidative stress, particularly those that target mitochondria, the main site for reactive oxygen species generation in all living organisms. **There is an increasing scientific, societal, and politic concern about pesticides within the One Health framework.**

In this context, **the challenge of the Action is to identify pesticides' adverse effects linked to oxidative stress that are relevant for both humans and ecosystems, and to describe the Key Events involved in these effects.** This **Pan-European network** will develop a new research strategy based on **Adverse Outcome Pathways (AOPs)**.

The Action will work within the One Health concept, **promoting interdisciplinary breakthroughs** between ecotoxicology, toxicology, bioinformatics, epidemiology and risk assessment. It will include scientists from academia, industry, regulatory agencies, a National Social Protection Scheme in charge of agricultural workers and operators, and Non-Governmental Organizations.

This Action will work in **collaboration with other international initiatives** (AOP-Wiki, PARC project) to implement science without duplication.

As there is an increasing interest of **New Alternative Methods** such as AOPs that has been identified as **keys areas of regulatory challenges**, the Action will **provide scientific input to the pesticide industry and regulatory agencies, disseminating science to a broad audience that include pesticide consumers, civil society, and policy makers.**

Areas of Expertise Relevant for the Action	Keywords
● Health Sciences: Environment and health risks including radiation ● Biological sciences: General biochemistry and metabolism ● Biological sciences: Systems biology ● Biological sciences: Metabolomics ● Biological sciences: Biodiversity, comparative biology	● pesticide ● oxidative stress ● AOP (Adverse Outcome Pathways) ● ecotoxicology ● toxicology

Specific Objectives

To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

<u>Research Coordination</u>

● To identify specific pesticide-induced OxS biomarkers relevant for both humans and key animal species relevant to the ecosystem level, using databases and literature analyses. The Action will achieve this by manual and systematic review using SysRev and by text mining approaches such as the AOP-helpFinder tool developed for AOPs.

● To use putative AOPs (Adverse Outcome Pathways) linking pesticide-induced OxS to several deleterious impacts on human and ecosystem health in order to contribute to understanding the link between pesticide modes of actions (MoAs) and adverse effect.

● To collect and compare methods and biological and/or computational models used to assess and explain the oxidative status in humans, animals, and ecosystems to provide an interdisciplinary dynamic around this issue. This RCO will promote exchange between different scientific fields: biology, eco(toxicology), bioinformatics, epidemiology, and regulation.

● To consider whether specific endpoints related to OxS in ecotoxicological assays could be used as indicators of adverse effects on human health.

● To propose a detailed database specification and knowledge extraction protocol to correlate the specific MoA of mitochondria disruption or OxS promotion by pesticides and putative AOPs linking pesticide-induced OxS to several Adverse Outcomes in (eco)toxicology, filing some gaps between academia and regulatory requirements.

● To identify gaps, drafting recommendations (testing strategies) to contribute to the development of new AOPs linking pesticide-induced OxS to different Adverse Outcomes.

● To consider the applicability of the resulting data in the context of exposure to pesticide mixtures.

● To contribute to the dissemination of scientific knowledge and methodological advances regarding pesticide (eco)toxicity, particularly in relation to (OxS), with a focus on cocktail effects and the identification of relevant biomarkers. This knowledge transfer will be directed towards industry stakeholders, policymakers, and regulatory agencies involved in the Plant Protection Products.

● To share knowledge among researchers and students from different fields and with different levels of experience. To improve dissemination of knowledge to pesticide users and healthcare professionals (in collaboration with occupational health and safety preventers) and the public.

Capacity Building

● Network Establishment: The Action will create a network involving researchers and innovators across various fields, including chemistry, QSAR, computational modelling, AOPs, toxicology, ecotoxicology, epidemiology, oxidative stress, pesticide MoA, risk assessment, and regulation. This initiative aims to promote diversity among disciplines, bridging gaps to achieve interdisciplinary scientific breakthroughs.

● Knowledge Exchange: The Action will foster knowledge sharing between different fields.

● Evidence-Based Approach: It will provide a robust framework for evaluating the role of oxidative stress (OxS) in pesticide toxicity and recommend designs for (eco)toxicological studies that consider low-dose mixtures and long-term exposure.

● Experimental Approaches: The Action will disseminate developed methodologies for assessing OxS in (eco)toxicology, encouraging innovative solutions in OxS evaluation.

● Youth Involvement: Young Researchers and Innovators (YRIs) will take on management roles, including Management Committee members and working group leaders, respecting gender balance.

● Communication Strategy: An active communication plan will be established to inform and educate the scientific community and the public, particularly in target countries, through training courses and institutional exchanges.

● Public Knowledge Transfer: The Action aims to transfer knowledge to a broad audience, including professionals, consumers, media, and policymakers, because the omnipresence of pesticides in our environment is a public health concern leading to various public debates.

● Funding Opportunities: The Action will provide the consortium, and potentially expanded groups, access to funding and infrastructure by applying for European project proposals to address identified gaps.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. SOUNDNESS OF THE CHALLENGE

1.1.1. DESCRIPTION OF THE STATE OF THE ART

Oxidative stress: a mechanistical link between ROS and several pathologies.

Oxidative stress (OxS) is defined as an imbalance between the cellular levels of antioxidants and pro-oxidants, including reactive oxygen and/or nitrogen species (ROS & RNS) (Fig. 1).

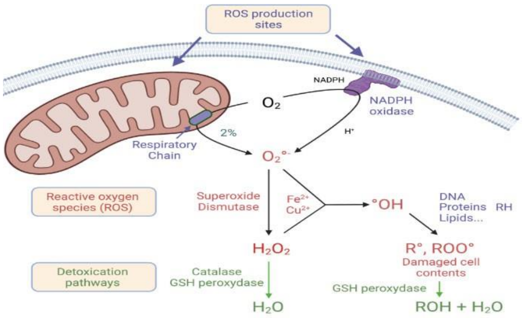

Fig. 1: Main reactive oxygen species (ROS) production sites and detoxification pathways.

ROS are mainly produced in the mitochondria, in peroxisomes, and in the endoplasmic reticulum (ER). Production of ROS is tightly regulated through cellular detoxication pathways: the activity of superoxide dismutase (SOD) generates hydrogen peroxide (H_2O_2) from the superoxide radical (O ˚-), which is then processed to oxygen (O_2) and water (H_2O) through the activities of glutathione peroxidase (GPX) or catalase (CAT). Under healthy physiological conditions, cells maintain a basal level of ROS to promote the balanced redox signalling required for various processes (cell metabolism, cell differentiation and survival, immune defence, modulation of transcription factor activity and the epigenetic marks) [1]. An increased ROS production can damage biomolecules, such as lipids, proteins and nucleic acids, and initiate senescence and apoptosis. The highly damaging nature of ROS has been known for several years, but their effects on vital organs are still of great interest. Although there are considerable gaps of knowledge in cellular damage, response mechanisms, repair processes, and disease aetiology in biological systems, the overproduction of toxic ROS is known to be responsible for a wide range of adverse health effects and diseases in humans, but also in ecosystems [1;2;3]. OxS is a key mediator of neuro-inflammation in central nervous system (CNS) disorders, such as Alzheimer's disease, multiple sclerosis, stroke and is also implicated in the emergence of functional deficits and disabilities [4]. Moreover, OxS is involved in obesity-related metabolic diseases and insulin resistance [5;6]. Both clinical and experimental studies have shown that antioxidant pathways are modulated during the progression of Metabolic-Dysfunction Associated Liver Disease (MAFLD) [7]. ROS are also involved in different stages of carcinogenesis by inducing DNA damage, altering proliferation and metastatic potential of tumor cells [1]. Concerning ecosystems, various classes of pesticides can affect both vertebrate and invertebrate species through OxS, leading for example to neurotoxicity and DNA damage or even mortality. In conclusion, as OxS is a joint key modulator of several pathologies both in ecosystem and human, this Action is focused on OxS in the frame of (eco)toxicology.

OxS: a key event in several established Adverse Outcome Pathway networks.

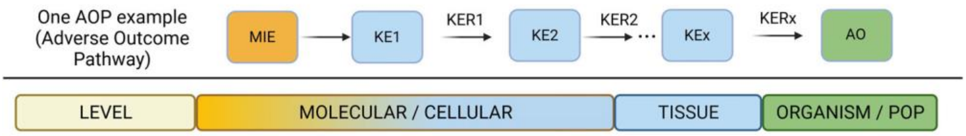

Fig. 2: Illustration of the Adverse Outcome Pathway (AOP) concept showing a causal cascade of Molecular Initiating Event (MIE) and cellular Key Event (KE) linking to a final adverse outcome (AO) at the population or organism levels. KEs are linked by Key Event Relationships (KERs) (Created with Biorender.com).

Molecular and cellular events can form a sequence of events leading to a pathology. This concept forms the basis of the **Adverse Outcome Pathways (AOPs)** framework, which organizes knowledge by describing causally connected sequences (Fig. 2) of essential molecular initiating events (MIE), key events (**KEs**) and key event relationships (KERs), finally resulting in an Adverse Outcome (AO) on health in humans or the wildlife. AOPs allow translation of mechanistic data into endpoints meaningful to ecological risk assessment such as survival, development, and reproduction in individual organisms and, by extension, populations [8]. AOPs also aim to provide modular and graphical representations that facilitate understanding of the (eco)toxicological effects spanning different layers of biological organisation (molecule, cell, tissue, organ, organism, population), interconnectedness to other AOPs/biological pathways, and lend themselves to discovery/building of modular, machine-learning amenable AOP networks [9;10]. Although AOPs are stressor-agnostic (which means that no chemical appears in the AOPs, they are generally developed for understanding and prediction of the potential adverse effects of chemicals that interact with a common molecular target; often such chemicals share certain chemical structure features [8]. AOP-Wiki is the collaborative online database where these AOPs are shared and updated (https://aopwiki.org/). OxS is involved in several AOPs, leading to adverse health outcomes, such as non-alcoholic steatohepatitis, liver cancer, developmental impairment in learning and memory, among others. A wide range of molecular/cellular endpoints, including cytochrome P450 (CYP) activation, glutathione oxidation, disruption of mitochondrial function, endoplasmic reticulum (ER) stress, or inhibition of fatty acid beta-oxidation can be identified in these AOPs. This Action will contribute to development and refinement of OxS-linked AOPs *via* use of New Approach Methodologies (NAMs) useful for safety assessment of chemicals and reduction of animal testing.

Pesticide exposure and human and environmental health.
Considering studies of professionals that handle or are in frequent contact with pesticides and who are *a priori* the most exposed, a recent report (https://presse.inserm.fr/publication-de-lexpertise-collective-inserm-pesticides-et-effets-sur-la-sante-nouvelles-donnees/43303/) conducted by the French Research Institute of Medical Research (INSERM), confirmed a moderate to strong presumption of a link between pesticides and non-Hodgkin's lymphoma (NHL) (occupational exposure (oe)), leukaemia (oe and residential exposure (re)), multiple myeloma (oe), tumours of the CNS (oe, re), visceral sarcomas (oe), kidney and bladder cancers (oe), and prostate cancer (oe, re). The INSERM report also confirmed the strong presumption of a link between occupational exposure to pesticides, and Parkinson's disease, cognitive disorders, and children anxiety. Moderate links were identified between pesticide exposure and Alzheimer's disease. For NHL, a strong presumption of a link was established with lindane, DDT and organophosphates (OPs) such as malathion and diazinon. For children, exposure to pyrethroids during embryonic and foetal stages was associated with the risk of internalised behaviour problems, such as anxiety. Experimental studies in rodents suggest that the immature blood-brain barrier is highly permeable to pyrethroids during early stages of development, supporting the biological plausibility of this link. Moreover, recent studies have shown that these insecticides also contaminate interior environments. Mother-child cohort studies point to a link between occupational or environmental organophosphate exposure during pregnancy and the risk of neuropsychological and motor development disorders in children. Metabolic changes after perinatal exposure to OPs were also described in new-borns [11]. Neonicotinoid or pyrethroid insecticides, glyphosate, or fungicides exposure may also support the development of metabolic diseases [12]. It is noteworthy that recent population studies have shown that consumption of organic food correlates with a significantly decreased risk of metabolic diseases and cancers [13;14]. Agricultural industrialisation and intensification are now recognised as a major factor governing the loss of biodiversity [15]. Outdoor application of pesticides through spraying or direct soil application inevitably implies that non-target organisms and ecosystems are also exposed. For example, OxS is known to play an important role in the neurological, reproductive, and developmental toxicity caused by pyrethroids towards fishes [2] and herpetofauna (reptiles and amphibians) [16;17]. Soil may be contaminated for long period; pesticides may leach into the groundwater, which may serve as a source of drinking water. Depending on their concentration and toxicokinetic properties in living organisms, pesticides may have several effects on non-target organisms through the induction of soil or organism microbiota dysbiosis. These effects may disturb the structure and functioning of ecosystems and the services they provide [18], leading for example to potentially harmful cyanobacteria blooms [19]. Aquatic ecosystems are particularly vulnerable and are the final receptacle of many anthropogenic pollutants and several studies demonstrated the toxicity of several pesticides (including mixtures) on different non- target organisms, such as microalgae and molluscs [20]. Although a mechanistic understanding of pesticide-induced ecotoxicity has received increasing attention in recent years, much remains to be explored. A recent scientific expertise conducted by two French Research Institutes, namely INRAe and Ifremer, has thus pointed out a lack of knowledge on "cocktail" effects, on services affected by pesticide pollution, and on potential impact on some less studied organisms, such as amphibians, reptiles, microbiota (https://www.inrae.fr/en/news/impacts-plant-protection-products-biodiversity-and-ecosystem-services-findings-inrae-ifremer-collective-scientific-expert-report). Moreover, many correlations between exposure to pesticides and human or ecosystem health were mainly reported for banned pesticides, it is therefore relevant to now focus research interest on the currently used pesticides for understanding and predicting their potential adverse effects. Among currently used pesticides, several contain active substances that

can induce ROS.

Pesticide-induced OxS linked to adverse effects in humans and ecosystems
Several experimental studies have reported the pro-oxidative properties of some insecticides, fungicides and herbicides. Indeed, these Active substances can induce ROS production through various mechanisms: (i) detoxification *via* cytochrome P450-dependent processes, (ii) direct and/or indirect effects on mitochondrial respiratory complexes, (iii) action on Sirt (Sirtuin)- and/or on the transcription factor Nrf2 (erythroid 2-related factor 2)-dependent antioxidant responses, (iv) changes in antioxidant enzyme expression and/or activity (v) impact on cellular levels of antioxidants, such as glutathione (GSH). Organisms have developed mechanisms to alleviate OxS by scavenging free radicals, but in case of excessive ROS production, the antioxidant capacity of individuals is overwhelmed, leading to an OxS imbalance that can induce toxic effects [21]. Among the toxic mechanisms of pesticides, OxS may interfere with inflammatory responses, metabolism and/or cell signalling involved in the control of growth and survival. Thus, increasing attention has been paid to the influence of OxS on pesticide- associated neurotoxicity, immunotoxicity, cardiotoxicity, hepatotoxicity, reproductive toxicity, genotoxicity, hematotoxic effects, and digestive system toxicity [22]. Furthermore, the tight interconnection between mitochondrial dysfunctions (and ROS production) and the epigenetic marks (through the availability of s-adenyl-methionine, acetyl-coA, succinate, fumarate) may support a role of pesticides in transgenerational inheritance of some human diseases [23]. Field studies have confirmed that OxS is induced in aquatic organisms by several classes of pesticides, such as organochlorines, organofluorines, OPs, carbamates, pyrethroids, bipyridyl herbicides, triazine herbicides, and chloroacetanilide herbicides [24]. Several OPs are persistent, whereas even very low concentrations have been found to be neurotoxic to both vertebrate and invertebrate aquatic animals through acetylcholinesterase inhibition [25]. Several studies have described the induction of OxS in fish treated with OPs. For example, dichlorvos was found to induce OxS in carp (*Cyprinus carpio*) and catfish (*Ictalurus nebulosus*), as well as in European eels (*Anguilla anguilla*). Other OPs may cause OxS, for example trichlorfon in Nile tilapia, methyl parathion in freshwater characid fish matrinxã (*Brycon Cephalus*), malathion in gilthead seabream [26]. Pesticides, through OxS, can also affect honeybees which are essential for the ecosystem maintenance and for plant production in agriculture [27].

OxS biomarkers linked to pesticide toxicity.
The Food and Drug Administration defines a biomarker of effect as an indicator of biological function changes due to chemical exposure [28]. Since diseases develop lately after exposure (e.g. Parkinson disease, cancer...), enhancing research on effect biomarkers can help predict long-term impacts. Various biochemical molecules serve as biomarkers of OxS and can be classified as molecules that are modified through ROS interactions and molecules of the antioxidant system that change due to redox stress [29]. GSH is a nonenzymatic antioxidant constituting the first antioxidant line of defence against ROS. Antioxidant enzymes, such as Superoxyde Dismutases (SOD), Catalase (CAT), and glutathione S-transferases (GSTs), are also considered to be sensitive OxS biomarkers. Enzymes gamma-glutamyl transpeptidase and paraoxonase-1 are often used as OxS biomarkers. The total antioxidant capacity (TAC) can also assess antioxidant status. Biomarkers related to oxidative damage include also molecules that are related to lipid peroxidation (e.g., malondialdehyde [MDA] and thiobarbituric acid reactive substances [TBARs]), protein damage (e.g. carbonylated proteins), and DNA damage (e.g., 8-hydroxyguanine: 8-oxodG). A study of pesticide-exposed workers, with oxidative status biomarkers including TBARs, 8-oxodG, GSH, oxidized glutathione levels (GSSG), revealed changes in biomarkers of oxidative stress and adaptive response to increase antioxidant response [30]. Another human study found advanced oxidation protein products and reactive oxygen metabolites as sensitive OxS biomarkers [31]. Ecotoxicology focuses on the OxS response after chemical exposure in microorganisms, especially those degrading pesticides, using various methodologies to measure OxS biomarkers. For example, research on pyrethroid toxicity in fish identified lipid peroxidation, GSH, glutathione reductase, GPX, GST, glutathione disulphide, SOD, CYP1A, CAT, inducible nitric oxide synthase (iNOS), ethoxyresorufin-O-deethylase, and MDA as OxS biomarkers (Review, see [32]). OxS biomarkers have been assessed in organisms other than vertebrates, such as microalgae (Review, see [33]). When OxS occurs, Nrf2 detaches from its inhibitor Kelch-like ECH-associated protein 1 (Keap1) and binds to the antioxidant response element (ARE) promoting gene expression of detoxifying enzymes and antioxidant enzymes. Xenobiotic exposition (in relation to OxS) leads to the Nrf2 pathway activation and is a common cellular stress response of many organisms from aquatic organisms to humans [34]. Thus, expression levels of its target genes can be used as OxS biomarkers [35]. Moreover, omics techniques are gaining attention in (eco)toxicology because they can assess the molecular and metabolic responses associated with AO of chemicals in animals and humans [36,37]. Oxidative stress is a mechanistic process at the crossroad of pesticide exposure and many human and ecosystem health disturbances. Numerous OxS biomarkers have been used to assess the ecotoxicological and toxicological effects of pesticides, with some being

similar in humans and wildlife.

1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Pesticide-induced OxS is suspected to play a central role in ecosystem disturbance and various pathologies in humans, including cancers, neurodegenerative diseases, and metabolic disorders. While the prooxidative properties of banned pesticides (such as OPs and organochlorines) have been well documented, several classes of approved pesticides, particularly those affecting mitochondrial functions (like ATP synthase and mitochondrial respiration), have also been found to disrupt oxidative status and could thus exert toxic impacts in non-target organisms. In this context, considering the high number of pesticides used and the subsequent potential cocktails present in the environment, it is an important challenge to improve knowledge on mechanisms of action of selected approved pesticides and to predict their potential long-term adverse effects when used alone and in cocktails. We will select those pesticides which, according to the scientific literature, have been shown to have pro-oxidative properties, including pesticides with Mode of action (MoA) which impacts mitochondrial respiration. The Action hypothesis is that pesticide-induced OxS is one of the main KE that links pesticide exposure and adverse effects in the One health (Oh) concept (Fig. 3).

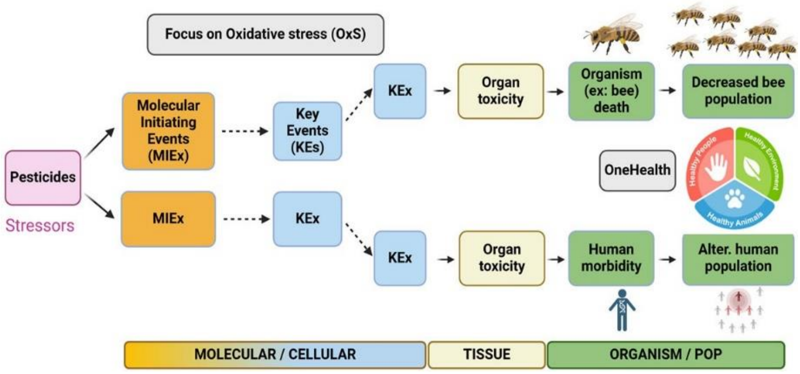

Fig. 3: Overview of the CAPSTONE Action. A way to bring together the available information, technologies, and concepts related to the link between OxS, AOP, and pesticides' adverse effects. The Action will be in line with the "one-health approach". The Action could facilitate risk assessment by the development of predictive human and environmental adverse effects (Created with Biorender.com).

The Oh concept has been in development since the beginning of the 2000s. It is an integrated approach recognising the interconnections between the health of humans, animals, plants, and ecosystems. This concept encourages collaboration, synergy, and cross-enrichment of all sectors and actors whose activities may have an impact on health. The aim of the **Action is to consider OxS as a cornerstone of the adverse effects of pesticides in humans and ecosystems and as a KE or a MIE in AOPs relevant for currently approved** pesticides whose prooxidative property has been shown. OxS and mitochondria are referenced respectively in 13 and 37 KEs of the AOP-Wiki database (https://aopwiki.org/). This **Action will use the AOP framework to strengthen the link between pesticides and OxS to better predict their adverse effects (Fig. 3).** Since pathologies develop lately after exposure (e.g. Parkinson disease), focusing research interest on effect biomarkers in humans and ecosystems of currently used pesticides will allow the prediction of their potential long-term impacts and help regulatory agencies in the pesticide registration processes that certify safe use of pesticides in Europe. This Action will contribute to 1/ identify pesticides and Key Events/Relationships linked to Oxidative Stress for pesticides 'adverse effects relevant in (eco)toxicology 2/ decipher mechanistic toxicology of pesticides 3/ improve prediction of toxicity (in particular for long-term exposure and exposure to many pesticides with potent cocktail effects) 4/ give inputs to the regulatory process for such compounds.

1.2. PROGRESS BEYOND THE STATE OF THE ART

1.2.1. APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE OF THE ART

Role of OxS and AOPs: Pesticide exposure leads to OxS mainly through 3 ways 1) their detoxification process, 2) their impact on the antioxidative defence, 3) their impact on complexes of the mitochondrial respiratory chain. Mitochondria, as a major site of ROS production is a specific target in the MoA of some groups of insecticides (acequinocyl, fenazaquin, fenpyroximate) and fungicides (SDHi, carboxamides, strobilurines) in target organisms. ROS production has also been described for herbicides, for example for gluphosinate [38]. Besides, OxS is one the KE of various AOPs. **Mutual contributions between AOP-Wiki database and the Action**: Numerous AOPs have been described in the AOP-Wiki database (https://aopwiki.org/). The AOP-Wiki database gathers all AOPs described by researchers (developed, under development or reviewed for endorsement), and these descriptions are organised into three distinct page types (Event, Relationship, AOP). OxS is referred as a KE (KE1392) in the database, but in fact, 13 KEs includes the keyword “oxidative stress” and consequently, information on this KE is scattered and potentially confusing, which is unhelpful for both writers and users of AOPs on OxS. There is no pooled analysis reviewing the link between OxS and the observed adverse effects in humans and ecosystems for pesticides. This Action therefore aims to i) gather all known information present in AOP-Wiki and in the scientific literature ii) enrich the database with data from the scientific literature not yet included in the described AOPs to strengthen the links between OxS and (eco)toxicological AOs for pesticides. In contrast to AOP-Wiki which is stressor-agnostic, the results of the Action will link pesticides to KE. **Database specification: Our Action will create a detailed database specification and design a protocol for extracting relevant knowledge form FAIR resources.** Research data must be managed in line with the FAIR principles to ensure that researchers can find, access and re-use each other’s data, maximising the effectiveness & reproducibility of research [39]. Several FAIR resources of interest have been identified [40;41], which support information extraction and synthesis, and thus paves the way for the construction of a first iteration of an OxS-AOP knowledge management system. The hosting and maintenance of the comprehensive database itself is a perspective to be executed beyond this Action. Thus, the goal of our action is to ensure data compliance with a complex regulatory landscape and provides tailored queries as a basis to build such resource in a FAIR manner. This implies that the organization and storage of data in the envisioned database should align with international regulations and allows for easy navigation through guidelines set by regulatory bodies, such as the EFSA, FDA, EPA, REACH or OSHA, especially when dealing with hazardous substances. The database specification and the reproducible and open-source building workflow will ensure adherence to the stringent requirements necessary for regulatory approval, thereby minimizing legal risks and enhancing the long-term Action’s overall credibility and success. **Evaluation of OxS:** Most of the methods used to assess OxS are based on the activation of antioxidant defences and measurement of cellular macromolecules damages (DNA, proteins, lipids). However, depending on the duration and intensity of the pro-oxidant stressor, antioxidant defences may only be induced during the first phase of the response, whereas in other conditions, organisms can exhibit no variations or transitory responses before adaptive mechanisms occur [42]. All these possibilities (and their combinations) have been reported, and this complexity of antioxidant responses to pollutants often leads to controversy about the use of OxS in (eco)toxicological applications, as reported by Regoli *et al.* [43]. Moreover, high reactivity of ROS makes OxS difficult to measure over time, and there is a need to share methods across scientific disciplines. Recent innovative methods are developed to predict the potential oxidative or anti-oxidative actions of various molecular actors from the host or the environment, such as pesticides. This Action will review these approaches, such as the real-time release of ROS (H_2O_2 and/or NO), the reactive probes for total and mitochondrial OxS (i.e. nonfluorescent dyes in a reduced state and fluorescent upon oxidation), the total antioxidant activity (ferric-reducing antioxidant power), or the activities of ethoxyresorufin dealkylase, methoxy- and pentoxyresorufin dealkylase and GST. In many studies a set of experiments was used to assess the capacity of a pesticide to generate OxS by measuring cytosolic and/or mitochondrial ROS, evaluating the GSH/GSSH ratio, and by measuring the expression/activity of antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. Some studies complete these parameters following mitochondrial functions by measuring oxygen respiration rate, the activities of mitochondrial complexes or the mitochondrial membrane potential. Furthermore, omics technologies (genomics, epigenomics, transcriptomics, proteomics, metabolomics) could be valuable tools to investigate the different molecular levels of OxS- activated pathways and also to elucidate the mechanisms of toxic actions (identifying proteins and/or metabolites as potential biomarkers of effects) associated with pesticide exposure, allowing straightforward assessment of the degree and chemical specificity of OxS. Comparative toxicogenomic database (CTD), CompTox Chemical Dashboard (https://www.epa.gov/chemical-research/comptox- chemicals-dashboard), proteomics and genomics data will be investigated as evidence-based approaches for OxS assessment and its relationship with disease development. CompTox Dashboard contains NAMs based empirical testing of thousands of chemicals and covers mitochondrial membrane potential and several endpoints indicative of OxS [44]. In conclusion, the Action will review the different biomarkers to analyse OxS in the frame of (eco)toxicology, as many options exist to study this KE. **Real-life scenarios**: Most studies on pesticide impacts report effects at doses far removed from real- life exposures in ecosystems or humans. In reality, individuals are continuously exposed to pesticide mixtures from various sources, including food, water, and air. Even low concentrations of individual pesticides deemed safe can have harmful effects on organisms [45]. Our Action will also address the non-exclusive issues of low doses and mixture effects of repeated and chronic exposure and highlight other applications of the AOP concept, such as its use in biomedical fields and epidemiological studies. **Ecosystems health and human health**: Useful data available from studies carried out on different species (e.g., fish, earthworms, amphibians) can be assessed to investigate whether some endpoints- biomarkers related to OxS are useful as indicators in human health. Pathway-based approaches to toxicity assessments have been demonstrated as viable alternative models to whole animals with regards to protecting human and ecological health [46]. Estimating biological pathway conservation across species relies on assessment of taxonomic relatedness notably by comparing target similarity, i.e. sequence and structure of gene or protein involved. This can be done using a combination of tools [46;47] such as Sequence Alignment to Predict Across Species Susceptibility (SeqAPASS) [48;49] and Genes-to-Pathways Species Conservation Analysis (G2P-SCAN). The action will review the extrapolation uncertainty between the human and eco-species both in terms of the MoA and the level of effect. With this, the action should address how these sublethal effects impact the function of identified ecosystems and how these can be extrapolated *via* AOP approaches to impacts on human health. In conclusion, there is a need to fill the gap of the MoA triggered by pesticides, implicating OxS using the AOP concept and in a Oh context. No pooled analysis of the various methods of assessing OxS has been conducted in recent years; therefore, there is no clear evidence of whether data derived from ecotoxicity studies can be used for humans and *vice versa*. This Action intends to enhance knowledge on (i) the role of OxS in the MoA of pesticides focusing on mitochondria disruption and several endpoints indicative of OxS, (ii) the AOPs associated with pesticides linked to OxS (including any missing pathways that should be incremented), (iii) applicable methods and models available for the quantitative measurement of OxS in both humans and ecosystems, and (iv) lessons from the ecosystem that can inform human health. Moreover, considering real- life scenario and bringing together leading experts in pesticide (eco)toxicology, this Action seeks to advance the field and provide valuable insights to regulatory agencies. The Action will also contribute to dissemination of knowledge to a large public and will increase the public awareness about the efforts made by the scientific community to protect human and environmental health.

1.2.2. OBJECTIVES

1.2.2.1. *Research Coordination Objectives*

The main challenges are 1) to identify pesticides' adverse effects linked with OxS and relevant for both humans and ecosystems, 2) to describe Key Events involved in these effects, 3) to characterize the gaps in the AOP-Wiki database and therefore to propose new AOPs related to OxS-based pathologies. This will strengthen the links between pesticides and OxS- based AOPs, contribute to mechanistic (eco)toxicology, better predict their adverse effects and give inputs to the EU regulatory process relative to stressors likely to trigger existing or new AOPs. This Action consists of 9 Research Coordination Objectives (RCOs), detailed below and illustrated in Fig. 4.

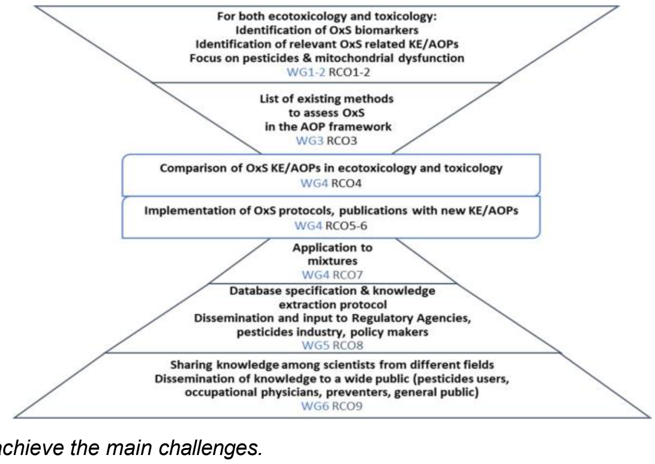

Fig. 4: Summary of the RCOs to achieve the main challenges.

RCO1: To identify specific pesticide-induced OxS biomarkers relevant for both humans and key animal species relevant to the ecosystem level, using databases and literature analyses. We will achieve this by manual and systematic review using SysRev and by text mining approaches such as the AOP-helpFinder tool developed for AOPs and other applications. **RCO2:** To use putative AOPs linking pesticide-induced OxS to several deleterious impacts on human and ecosystem health in order to contribute to understanding the link between pesticide modes of actions (MoAs) and adverse effect. We will focus on currently applied pesticides whose modes of actions are linked to the impact on mitochondrial respiration or to other endpoints related to OxS in both humans and ecosystems. This RCO will also be achieved though the analysis of the literature and databases. **RCO3:** To collect and compare methods and biological and/or computational models used to assess and explain the oxidative status in humans, animals, and ecosystems to provide an interdisciplinary dynamic around this issue. This RCO will promote exchange between different scientific fields: biology, eco(toxicology), bioinformatics, epidemiology, and regulation. **RCO4:** To consider whether specific endpoints related to OxS in ecotoxicological assays could be used as indicators of adverse effects on human health. The indicators can be "direct" indicators for human health if they are extrapolated from ecosystem indicators to human. They can also be "indirect" considering the Oh concept and relationship between ecosystem health and human health. **RCO5:** To propose a detailed database specification and knowledge extraction protocol to correlate the specific MoA of mitochondria disruption or OxS promotion by pesticides and putative AOPs linking pesticide-induced OxS to several Adverse Outcomes in (eco)toxicology, filing some gaps between academia and regulatory requirements. **RCO6:** To identify gaps, drafting recommendations (testing strategies) to contribute to the development of new AOPs linking pesticide-induced OxS to different Adverse Outcomes. **RCO7:** To consider the applicability of the resulting data in the context of exposure to pesticide mixtures. **RCO8:** To contribute to the dissemination of scientific knowledge and methodological advances regarding pesticide (eco)toxicity, particularly in relation to oxidative stress (OxS), with a focus on cocktail effects and the identification of relevant biomarkers. This knowledge transfer will be directed towards industry stakeholders, policymakers, and regulatory agencies involved in the Plant Protection Products (PPP) authorization process, with a broader extension to actors engaged in other regulatory frameworks, notably REACH (Registration, Evaluation, Authorisation, and Restriction of Chemicals) and the Biocidal Products Regulation (BPR). By leveraging the AOP framework, the compilation and integration of mechanistic data related to pathophysiological pathways that underlie the (eco)toxicity of chemicals and notably pesticides, will help to support, refine and/or improve risk assessment methodologies and regulatory registration processes in Europe. This will contribute to well-informed decision-making processes, potentially leading to more effective regulatory measures and safer use practices. Moreover, interconnection with adequate risk mitigation measures, i.e. prevention- minimisation of exposure of non-target organisms and/or to propose alternative solutions to protect crops from relevant pests and plant diseases will be proposed. This can support sustainable agriculture and food security thereby safeguarding the farmers' health (the primary users of pesticides) and citizens living nearby, people exposed through food diet, and ecosystems' health. **RCO9:** To share knowledge among researchers and students from different fields and with different levels of experience. To improve dissemination of knowledge to pesticide users and healthcare professionals (in collaboration with occupational health and safety preventers) and the public. Organization of collaboration activities [communication activities: newsletters, webinars, workshops, conferences, Working Group (WG) meetings, training schools, short-term scientific missions (STSMs), writing of international recommendation and reviews] on the above-mentioned objectives will allow the consortium to achieve these objectives to respond to the main challenges. In addition, a non-profit scientific foundation, involved as a partner in the Action, has experience in disseminating scientific information to the general public through (1) an original monthly radio program (2) the organisation of monthly conferences for the general public with an invited researcher, available on Youtube with a large audience and (3) the creation of original podcasts immersed in research laboratories. This Foundation is also used to organising live conferences and webinars. This Action will, for the first time (i) consolidate and extend results from ecotoxicology to human toxicology, (ii) contribute to the development of new AOPs focused on pesticide-induced OxS, (iii) disseminate science to a large public (regulatory agencies, consumers, and pesticide users, occupational physicians...).

1.2.2.2. *Capacity-building Objectives*

The 9 RCOs can only be realized through a multidisciplinary and multi-sector research network:

- **Network Establishment**: The Action will create a network involving researchers and innovators across various fields, including chemistry, QSAR, computational modelling, AOPs, toxicology, ecotoxicology, epidemiology, oxidative stress, pesticide MoA, risk assessment, and regulation. This initiative aims to promote diversity among disciplines, bridging gaps to achieve interdisciplinary scientific breakthroughs. This coordination objective is to achieve a critical mass of people from various research and scientific fields through the consolidation of a dynamic network of researchers and risk assessors involved in assessing the risk of pesticides for both humans and environment.
- **Knowledge Exchange**: The Action will foster knowledge sharing between different fields.
- **Evidence-Based Approach**: It will provide a robust framework for evaluating the role of oxidative stress (OxS) in pesticide toxicity and recommend designs for (eco)toxicological studies that consider low-dose mixtures and long-term exposure.
- **Experimental Approaches**: The Action will disseminate developed methodologies for assessing OxS in (eco)toxicology, encouraging innovative solutions in OxS evaluation.
- **Youth Involvement**: Young Researchers and Innovators (YRIs) will take on management roles, including Management Committee members and working group leaders, respecting gender balance.
- **Communication Strategy**: An active communication plan will be established to inform and educate the scientific community and the public, particularly in target countries, through training courses and

institutional exchanges.
- **Public Knowledge Transfer**: The Action aims to transfer knowledge to a broad audience, including professionals, consumers, media, and policymakers, because the omnipresence of pesticides in our environment is a public health concern leading to various public debates.
- **Funding Opportunities**: The Action will provide the consortium, and potentially expanded groups, access to funding and infrastructure by applying for European project proposals to address identified gaps.

The Action will include:
- **Expanded Network**: Development of a larger network beyond the consortium, encouraging contributions from researchers in toxicology and ecotoxicology to AOP approaches.
- **Diverse Partnerships**: One National Agency for Food, Environmental and Occupational Health & Safety, one company specialized in regulatory procedures which supports over 1,300 EU companies to ensure regulatory compliance for the market introduction, and academic scientists involved in policy- making (with many participants being European Registered Toxicologists). One National Social Protection Scheme in charge of agricultural workers and operators and especially the department of occupational and health safety known for its quality of the service provided to the affiliates and its prevention actions deployed in the rural field, in many sectors of activity.
- **NGOs Partnerships**: One NGO focused on environmental transition and biodiversity to disseminate knowledge to pesticide industries and advocate for better awareness among decision-makers and the public and one non-profit scientific foundation, which has experience in international conference organization and in disseminating scientific information to the general public.
- **Interdisciplinary Training**: Establishing and delivering training schools and short-term scientific missions (STSMs) for YRIs and other stakeholders on topics related to (eco)toxicology and AOPs.
- **Support for Inclusiveness**: Providing conference grants to researchers from Inclusiveness Target Countries (ITCs) to enhance interdisciplinary knowledge sharing.
- **International Conference**: Organizing an international conference to share knowledge with a wide audience, including civil society, pesticide users, industry representatives, and policymakers, facilitated by a foundation experienced in organizing such events.
- **Geographic Diversity**: The Action includes 68 participants from 17 countries, focusing on geographic diversity, with participation from Central and Eastern Europe, Northern Europe, Southern Europe, including 8 Inclusiveness Target Countries (ITCs). One near neighbour country (NNC) (Kosovo) and one Cost International Partner (2 members from the United States of America) are also partners of the Action. As the omnipresence of pesticides is a worldwide health problem (with sometimes significant geographical differences in term of exposure), and OxS in (eco)toxicology is a well-researched area worldwide, participation from other NNCs or ITCs is expected over the duration of the COST Action. Further opportunities will be explored over the tenure of the Action through existing partnerships and newly established collaborations that will arise from the Action’s activities.

The Action will adhere to COST guidelines for efficient management and training organization, prioritizing participants from ITCs for short-term scientific missions. Gender balance is a priority, with a current composition of 40% males and 60% females, and efforts will be made to maintain this balance throughout the Action. The Action promotes careers, including a significant representation of young researchers and innovators (21 YRIs, 31% of total members) interested in NAMs development in (eco)toxicology.

2. NETWORKING EXCELLENCE

2.1. ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

2.1.1. ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

There are relevant European and international research interests on the role of OxS in the development of pathologies, including the Canadian OxS Consortium, COST Action CM1201 Biomimetic radical chemistry, COST Action BM1203 (EU-ROS) dedicated to providing new insights and tools for better understanding redox biology and medicine, and NutRedOx COST Action (CA16112) involved in the study of biological redox-active food components that are relevant to the aging organism and its health, function, and vulnerability to disease. Another European consortium, CA18221 (PERIAMAR), aims to analyse the available information and design an environmental risk assessment protocol safe enough to protect amphibians and reptiles from pesticide impacts. There are also European WGs on AOPs that aim to bring together AOP-structured information in several topics, such as the identification of endocrine disruptors. For example, the group EURION (European Cluster to Improve Identification of Endocrine Disruptors) has an AOP WG that aims to support and facilitate AOP- related activities in EURION projects and bring together AOP-structured information and data across different projects. In addition, the European Partnership for the Assessment of Risk from Chemicals (**PARC**) was recently developed in the frame of Horizon Europe. This is an EU-wide research and innovation program to support EU and national chemical risk assessment and risk management bodies with new data, knowledge, methods, networks, and skills to address current, emerging, and novel chemical safety challenges. In the frame of PARC, new AOPs will be developed, among other activities, and the existing knowledge will be reviewed and utilised to facilitate the uptake of new approaches (including the AOP framework) in regulatory science. While the above European and research interests are focused either on OxS, AOPs or the assessment of risk for chemicals, separately, to the best of our knowledge, there are no European consortia in the field of OxS in relation to the AOP framework and pesticide effects in a one health context. For example, in PARC, several speciality groups are focusing on the development of AOPs (or the identification of gaps) related to neurotoxicity, immunotoxicity, metabolic/endocrine disruption or non-genotoxic carcinogenesis but none are specifically focused on OxS as a key event involved in related Adverse Outcomes. Moreover, ecotoxicological aspects are not overrepresented in the first years of PARC as the partnership mostly builds on work undertaken in the EU program HBM4EU (Human Biomonitoring for Europe), which ended in 2022, and will broaden its scope of interest to environmental risk assessment later in the Action. This Action may therefore support PARC with preliminary works on a KE which could easily be connected to many (eco)toxicological outcomes. The Action will provide crossover environmental and human health data and allow the scientific community and society to consider the interdependency between human and ecosystem health. The Action is innovative in promoting multidisciplinary and global approaches aiming to manage a scientific issue that combines the adverse effects of pesticides, OxS, and the AOP framework in a one health context at both conceptual and technical levels. The Action will also aim to illustrate how ecotoxicological indicators can aid in understanding and predicting the impact of pesticides on human health. In addition, the Action (i) will promote interaction between ecotoxicologists and toxicologists; (ii) highlight innovative methods to assess OxS that can be applied in both humans and ecosystems, allowing predictions of the potential oxidative or anti-oxidative actions of pesticides and, thereby, various molecular actors from the host or environment; (iii) and will be a driving force behind the AOP framework, especially for the assessment of pesticide effects and considering realistic doses and long-term exposure.

2.2. ADDED VALUE OF NETWORKING IN IMPACT

2.2.1. SECURING THE CRITICAL MASS, EXPERTISE AND GEOGRAPHICAL BALANCE WITHIN THE COST MEMBERS AND BEYOND

This Action will gather scientific expertise in the different fields of pesticides, AOPs, OxS, in the frame of (eco)toxicology. Currently, research groups working on these issues are fragmented over Europe and there are no opportunities for scientists with different disciplinary backgrounds to meet and coordinate their research efforts not only in the EU, but also in neighbouring countries and even the USA. **The initial critical mass of expertise is already present in the consortium** with a wide range of experience and covers all scientific fields required for the Action to accomplish the proposed objectives. The multidisciplinary network already includes 68 scientists from Universities or Research Institution), one private company specialized in Regulation Procedures, one NGO specialized in environmental transition and biodiversity and one Foundation specialized in health & environment, one National Agency for Food, Environmental and Occupational Health & Safety, one National Social Protection Scheme in charge of farmers and agricultural employees. All of which are qualified to design, perform, and evaluate toxicological studies, use (eco)toxicological models and methods, and perform exposure and risk assessments for both humans and the environment. The Action integrate Partners from broad geographic areas all over Europe (including 8 Inclusiveness ITCs), one NNC and one Cost International Partner. The consortium combines balanced skills in the fields of (eco)toxicology with expertise in biology (especially OxS), chemistry, bioinformatics, QSAR, computational modelling, AOPs, physiology, medicine, toxicology, human biomonitoring, epidemiology, mechanisms of action of pesticides, pesticide risk assessment, regulation. Stakeholders are interested in human disease, biodiversity, adverse effects of pesticides, OxS, and AOPs as described above. The proposers have authored a significant number of scientific papers, books, technical solutions, and patents, and attended and lectured at many renowned conferences, such as Eurotox, International Congress of Toxicology, and the Society of Environmental Toxicology and Chemistry. Some proposers participate as experts in different EU or local scientific bodies, and the proposers participate in several national, European research projects or COST Action as coordinators or task leaders. In addition to collaboration within academia, the proposers have long-lasting collaborations with industry partners. One company specialised in regulatory support for international and European industries is partner in the Action. A non-profit organisation (Foundation) in the field of health & environment, recognised as being of public utility, is also part of the consortium. The missions of this foundation are to support research in health and environment, with a strong orientation towards the fields of ecotoxicology and environmental toxicology, and to ensure the up-to-date dissemination of these research results to citizens. The Foundation also has the mission to favour constructive collaboration between the various actors in the health-environment field (e.g., researchers, elected representatives, companies, citizens, companies, farmers, governmental and non-governmental institutions) to facilitate the dialogue and set up concrete and efficient partnerships and stimulate dissemination of knowledge to a wide audience. The Action will be open and attractive for further growth of the consortium, especially thanks to the activity of members (from academia, one Foundation, NGO, one Social Protection Scheme in charge of farmers and agricultural employees and one Regulation Agency), one company specialized in regulation and its network and from experts involved in assessment committees of regulatory agencies dedicated to chemicals and pesticides (ECHA and EFSA activities).

2.2.2. INVOLVEMENT OF STAKEHOLDERS

Each partner will provide its own expertise at the conceptual and technical levels in the field of OxS, biomarkers of pesticide effects, OxS measurement, AOP development, risk assessment, (eco)toxicology to achieve the 9 RCOs. The network of Action consists of 68 participants (from 30 institutions from academia, one company, one regulatory agency, 2 NGOS and one Social protection scheme) with complementary skills. There is no risk of overlaps or divergences in the role of stakeholders since each has its specific scientific background. Balanced knowledges of the network will provide strong background for the achievement of the objectives**:** 23 members have relevant experiences in ecotoxicology and 33 in toxicology; 16 teams have expertise on pesticide-effects and their mechanisms of action; 21 teams have expertise on the methods for OxS assessment, characterisation of biomarkers (e.g., mitochondria stress) or omics approaches. 15 teams have expertise in use and/or development of AOPs.
RCO1 will be reached thanks to the collaboration between 20 teams (including one regulatory agency and company) that **(i)** have expertise related to OxS and/or mitochondrial respiration in *in vitro* and *in vivo* human, animal, or ecosystem related models, studying OxS biomarkers (**ii**) have experience in pesticide toxicity/MoA. **RCO2** will involve 21 members having experience in AOPs in predictive methods, predictive modelling, computational, bioinformatics and QSAR. **The RCO3 and RCO4** will be achieved through the collaboration between 25 teams (including one Foundation and one regulatory agency) who have developed research activities in methods for OxS assessment, OxS biomarkers characterization, evaluation of cellular antioxidative capacity pesticide chemistry, and omics approaches. The partners will collect and compare methods and biological models used to assess the oxidative status in humans, animals, and ecosystems. They will also propose a way to transpose its approaches on ecosystem samples. The **RCO5** will be achieved through the collaboration between scientists from academia, one National Regulatory Agency already involved in the Action and one company specialized in Regulatory compliance and environmental compliance. For the **RCO6**, all the stakeholders are invited to write recommendation and scientific papers related to pesticide (eco)toxicology and the link with OxS and AOPs in humans, pesticides vs. neurodegenerative disease/metabolic disease/cancer, long-term low-level exposure to pesticides vs. OxS induction, and pesticide mixtures vs. OxS induction/health disorders. **RCO7** and **RCO8** will be achieved through the collaboration of a network led by a company specialising in regulatory services for key EU markets. This company supports over 1,300 EU companies (46% large, 24% medium and 30% small) to ensure regulatory compliance for the market introduction of substances, mixtures and articles. The industries supported cover several critical sectors, including chemical manufacturing, aerospace, defence, electronics, energy, biocides, detergents, pharmaceuticals, medical devices as well as textiles, food supplements, cosmetics and personal care products. Through this collaboration, the company facilitates streamlined market access and ensures compliance with complex regulatory frameworks, thereby enhancing the competitiveness of EU companies in these strategic industries. Moreover, 24 participants who are experts in National or International agencies links to pesticides regulation will contribute to this RCO. 12 people are **European Regulatory Toxicologist**. This consortium will allow the Action to be relevant regarding the needs of regulatory agencies and industry and to communicate easily with them and policymakers. **All partners** will be involved in **RCO9**. At least 11 stakeholders (including a Foundation) have extensive experience with organizing meetings and workshops and have already co-chaired major international meetings with excellent understanding of logistic challenges**.** The **Foundation** will develop and support innovative actions in favour of integrative methods in (eco)toxicology to assess the effects of pollutants through their expertise in the field of biomarkers & biodiversity and will provide strong expertise to assess the relevance of the use of biomarkers (species/biomarker combinations) for environmental issues. One partner, which is a **National Social Protection Scheme in charge of agricultural workers and operators** have a strong experience in

communication to this population category, occupational physicians, healthcare professionals and preventers, will be particularly involved in this RCO. The organisation of training courses will also be carried out by young and senior scientists or professors experienced in (eco)toxicology or in AOPs, or in oxidative stress. Twenty-two members of the consortium are Professor or Assistant Professor. Moreover, one non-academic partner has already organised a national workshop on the thematic of AOPs & computational strategy to explore new perspectives in ecotoxicology, bringing together toxicologist and ecotoxicologist. In line with this workshop, stakeholders will organise an **international workshop on AOPs** to bring together the community of researchers interested in working to identify issues of interest in (eco)toxicology for the development of an AOP. Young Researchers and Innovators (YRIs) will also take leading positions in WGs, especially in coordinating the writing of reviews or participating in Short-Term Scientific Missions STSMs. YRIs will also be invited to participate in meetings and STSMs. Dissemination of scientific results will be achieved through workshop organisation, training courses, scientific recommendation papers (published in open-science), reviews (published in open-science), and through webinars and conferences for the public especially for the consumers, farmers and/or the occupational physicians.

3. IMPACT

3.1. IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAKTHROUGHS

3.1.1. SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

The Action will be in support of the Pollution Prevention and Control aims of the Green Deal to better elucidate the concept of Do No Significant Harm principle. The Action, focused on pesticides and OxS, can build on the European PARC project (ANSES (France) Horizon Europe (2021-2027)) for further development on (i) OxS as KE in AOP for other chemicals than pesticides (ii) other KE than OxS. Thus, the Action will also support the realisation of the Chemicals Sustainability Strategy (CSS) as part of the Green Deal.

Scientific: The Oh concept is emerging with growing interest. A broad field of expertise is needed to address this topic. Today, the research community working on AOPs and pesticides is still fragmented with communication gaps between ecotoxicology and toxicology. The multidisciplinary composition of our consortium and the Oh framework of the present Action will contribute to filling this gap. The Action will report and compare the various conceptual and technical approaches used to assess the role of OxS from pesticides in the frame of AOPs at both the human and ecosystem levels. AOP-based approaches will be applied in order to investigate the loss of biodiversity and human pathologies (e.g., metabolic, and neurodegenerative diseases and cancer). The Action will contribute to understanding the link between pesticide (insecticide, herbicide, fungicide) MoAs, their chemical structures, and OxS within the frame of AOPs. The Action identify biomarkers of adverse effects of pesticides linked to OxS at both ecosystem and human levels. The Action will identify and fill gaps in the field and lead to new ideas and/or research questions, increase research efficiency, and avoid overlaps due to harmonised procedures, and communication through networking events. The Action will contribute to raising a generation of young scientists with molecular-level expertise in the fields of (eco)toxicology.

Technological: This Action will have an impact *via* the in-depth understanding and clarification of AOPs and associated methods. This Action will identify and gather the experimental strategies and methods available in the field of biomarkers of the adverse effects of pesticides and biomarkers of OxS, and highlight those that can be applied at both the ecosystem and human level. The Action will create website dedicated to the issue to help coordinate the network activities. The Action will lead to the development of innovative approaches in the fields of pesticide (eco)toxicology. The Action will elucidate OxS-based AOPs for several pesticides (mainly insecticides and fungicides) and their mixtures. Relevant mixtures can be selected based on Pesticides and their residues in environmental samples (surface water & soil mainly).

Socio-economic: Data from the Action will be useful for agencies involved in risk management, as they will be highly complementary to the classic (eco)toxicological studies. The action will illustrate the relevance of OxS-based AOP *via* use of NAMs in toxicology and Integrated Approaches for Testing and Assessment (IATAs) which comprise a range of *in silico* tools, useful for safety assessment of chemicals and reducing animal testing. Pesticides are considered to be risk factors for human health and biodiversity, and the Action will provide answers to societal questions through communication to the general public and policy makers/regulatory bodies. The Action will be in support of the Pollution Prevention and Control aims of the Green Deal to better elucidate the concept of Do No Significant Harm principle by providing a focus on OxS. Moreover, the work is in support of the European PARC *via* our in detailed focus on OxS. The Action will contribute to increasing the public awareness about the efforts made by the scientific community to protect human and environmental health from pesticide exposure.

3.2. MEASURES TO MAXIMISE IMPACT

3.2.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

Knowledge creation: The Action will provide a complete review of the state of the art for methodologies and help harmonise various technical and conceptual approaches within toxicology and ecotoxicology (RCO1-2-3-4). The complementary expertise of the network will provide a global vision, generate new ideas, and identify and fill knowledge gaps. This Action will allow the implementation of OxS protocols, publication with new KEs and AOPs to bring out the human pathologies and biodiversity damages including (RCO5-6) development of predictive methods to address environmental and human hazards of mixtures (RCO7). The action will also specify the requirements of an open database on pesticides, useful for academia and Regulatory Agencies (RC08).
Transfer of knowledge: The Action aims at actively contributing to international (eco)toxicology congresses, publishing meta-analyses and reviews, and specify a database (RCO5-6). The action will also give input to pesticides industry, Regulatory Agencies and policy makers (RCO8) and dissemination knowledge to a wide public (pesticides users, occupational physicians, public) (RCO9). Transfer of knowledge and dissemination between countries and scientists will be support by STSMs, training schools, technical schools (with specific content derived from the activities of the WGs to build up their knowledge in the field of the Action). The Action will provide a unique coordinated platform for training capacity building and networking on OxS, the adverse effects of pesticides, and AOPs, and will lead to interdisciplinary interactions in a one health context.
Career development: 21/68 members of the consortium are YRIs. The network will provide them the opportunity to structure their future careers by improving their research skills with an integrated approach in the fields of OxS, AOPs construction, and the one health concept. The Action will also prioritise exchanges between young scientists from participating research groups in member countries of the COST Action, as well as STSMs and training schools. Importantly, they will be involved in leading positions in WG organisation and management. Similarly, for all leadership positions within the Action, specific care will be taken for equal distribution of leadership tasks involving gender equality and ITCs. The Action will contribute to increasing the presence of female researchers in international teams and the participation of young scientists. Young scientists will also be invited to participate in the COST Action meeting and training schools as invited speakers.

3.2.2. PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

Pesticides are considered to be a risk factor for human, animal, and ecosystem health. The omnipresence of pesticides is a societal, political, economic, medical, and scientific matter, and scientists should provide a link by communicating on this subject. The Action will help fill the large communications gaps between academic scientists, risk assessors, pesticides users and the general population and aim to support public policies. The results from the Action will be disseminated not only through open-access peer-reviewed scientific papers, but also through publication in more popular scientific and technical journals and webinars for occupational physicians & healthcare professionals and preventers. Our data will also be disseminated to National Competent Authorities for pesticide risk assessment and European agencies in charge of chemical safety. Communication will be also performed using website and social media, popular science media and one conference dedicated to a general public. In order to disseminate and create some dedicate times for dialogue and exchange, two webinars will be organized and a replay will be available at the end on the website.

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

The Management Committee will focus on enhancing communication between Working Groups (WGs), with Short-term Scientific Missions further facilitating collaboration. Regular meetings will be held to ensure coordination both within and between WGs, with each WG managed by two leaders to achieve their deliverables effectively. These meetings will clarify the missions, deliverables, and timelines, while intermediary and final meetings will ensure that goals are met. Training school organization will be discussed early in the WG activities to incorporate diverse expertise and disciplines. Co-authors of scientific publications will include all relevant stakeholders from each WG.

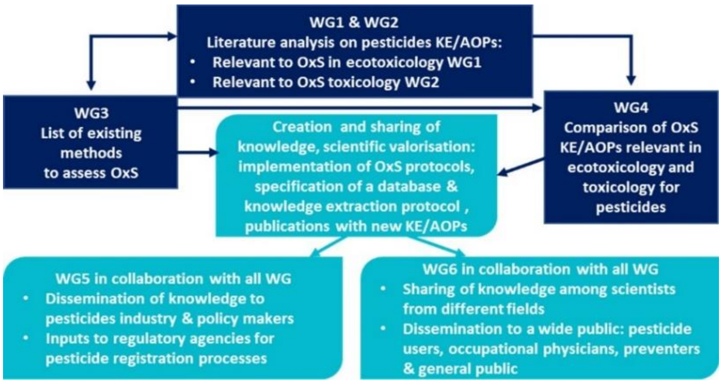

Fig. 5: Working groups organization showing their interconnection to facilitate the flow of information, sharing, creation of knowledge and dissemination

A kick-off meeting will be held at the start of the Action, featuring joint coordination by a man and woman scientist to promote gender balance. This meeting will establish a management committee, outline WG leadership (favouring early-stage researchers, ITCs, and gender balance), and allocate WG activities. Coordination among WGs has been pre-discussed and will be confirmed during this meeting. Each WG will have a designated leader responsible for Action dissemination (publications, website) and communication with stakeholders. Workshops on topics such as oxidative stress (OxS) in (eco)toxicology and AOPs will be organized by the coordinators of WGs 1, 2, 3, and 4. The planning of training courses will also be addressed at the kick-off meeting. An annual plenary meeting of the COST Action will be held, with the possibility of additional satellite meetings and workshops within and between WGs as needed. Communication activities will include workshops and congresses, inviting research teams from ITCs, NNCs, and international partners to encourage their involvement in the consortium. The organization and interconnection of WGs are detailed below and illustrated in Fig. 5.

WG1 & 2: Identification of AOPs relevant to OxS in ecotoxicology and toxicology. This WG aims at achieving RCO1 and RCO2**.-** *1) To identify specific OxS biomarkers related to pesticide-induced OxS relevant for both humans and key animal species relevant to the ecosystem – 2) to use putative AOPs linking pesticide-induced OxS to several deleterious impact on human and ecosystem health”* and at preparing WG3. The network will focus its interest on pesticides which primary site of action is the mitochondria (ATPase inhibitor, mitochondrial complex III or I electron transport inhibitors) or which impact other endpoints relative to OxS. These WGs will use existing AOPs to highlight OxS among identified KEs or MIE from ecotoxicological (WG1) and toxicological scenarii (WG2); these WGs will also perform a literature analysis related to human and animal/ecosystem heath to highlight OxS responding pathways and thus biomarkers. Periodic meetings and workshops between stakeholders involved in these WGs will allow to exchange data from ecotoxicology and toxicology approaches.

Tasks: The 3 tasks indicated below are identical for WG1 & 2 but will be simultaneously performed by **WG1 & 2**: T1.1 & T2.1 Identification of biomarkers for OxS that can be considered specific for model animal ecosystem or human. Biomarkers will be derived by AOP key events and by literature search since identification of biomarkers based solely on AOPs may not always be feasible. Thus, 10 teams (ecotoxicological part) and 10 teams (toxicological part) will carry out an in-depth analysis of the literature and databases using precise keyword algorithms to avoid redundancy between the various involved teams. Toxicological and ecotoxicological meetings and workshops will be organized between the stakeholders to pool the resulting data and highlight relevant OxS stress biomarkers. Moreover, interactions (meetings and workshops) between ecotoxicologists and toxicologists will be planned to allow sharing and comparing the data to prepare the achievement of **RCO4.** T1.2 & T2.2 Identification of AOPs relevant to OxS and ecosystem or human health. This task implies a collaborative work between teams having a background experience in AOPs, in oxidative stress biomarkers and in human or ecosystem health. First, the involved stakeholders will benefit from the findings of task 1 with regard to OxS meaning, concept, characterisation, and associated markers. OxS is included as a key event in established AOPs that are relevant for pathologies. Stakeholders will thus in a second step identify the various OxS biomarkers linked to identified AOP though the analysis of the literature and databases. This will bring out the human pathologies and biodiversity damages (at the species level along the AOP and also when possible, at the population and ecosystem levels) that could be linked to an AOP through OxS. The toxicogenetic effects and pathways of OxS are relatively well-described in human toxicology; therefore, we will use them as a starting point for hypothesis testing pathways and the initial steps of the AOPs in environmental toxicological analysis using, for example, the Computational Toxicogenomic Database and Reactome to build hypotheses based on genetic similarities and ortholog database analyses. T1.3 & T2.3 Identification of AOPs relevant for pesticides. We will focus our interest on compounds whose prooxidant property has been already described in untargeted organisms (both human and ecosystem). An updated list of the currently used pesticides in Europe will be provided by stakeholders involved as experts in public health risk assessment. Then, a literature analysis jointly performed during a workshop with relevant stakeholders will identify, which pesticides have already been confirmed to impact the same target organisms (human and ecosystems). Researchers will also suggest some recommendations to perform research on pesticides to address the lack of knowledge. In the case of lack of experimental and/or relevant data, modelling would help to predict a possible link between the pesticide with an AOP relevant to OxS. A group of researchers having good expertise both in pesticide MoA and OxS will work together on this issue. These tasks, linking pesticides MoA and OxS, will contribute to the specification of a database and the design of information extraction queries **(RCO5).** T1.4 Identification of gaps in the existing AOPs and recommendations. This task will be the topic of a special workshop to which participants of tasks 1, 2 and 3 of the WG1 and 2 will be invited. This task will allow to draft recommendations to contribute to the development of new AOPs linking pesticide-induced OxS to different Adverse Outcomes (**RCO6**). Exchanges with PARC on the development of new AOPs are planned. T1.5 Identification of candidates for training courses on the above-mentioned issues; STSM and ITC Conference Grants to stimulate them to apply for support.

Deliverables: D1.1 Website creation, D1.2 & D2.2 WG meetings, D1.3 Workshop on tools useful for systematic review and text mining on AOP, D1.4 & D2.4 Reviews of OxS biomarkers relevant for OxS model animal, ecosystem or human, D1.5 & D2.5 Training schools, D1.6 & D2.6 STSMs, D1.7 & 2.7 Reports on achievements, D1.8 Review on identification of AOPs linking pesticide-induced OxS to several pathologies, D1.9 Report/publication with the results of the pooled analysis of existing data, D1.10 Report on the identification of gaps and recommendations for progress, D1.11 WG meetings/communication to the science community and society.

WG3: Existing methods to assess OxS in the AOP framework and further needs: This WG aims at achieving RCO3. **Tasks:** Stakeholders that have experiences in OxS assessment will work together to propose a list of validated approaches used to evaluate OxS based on a literature search and then this WG will:

T3.1 Characterize methods used for measuring OxS, identify experimental models, evaluate sample types, and sample preparation methods. T3.2 List of existing methods used to assess OxS in the AOP framework. T3.3 Assess relevant Omics' approaches for the identification of OxS biomarkers and OxS-related effects. T3.4 Identify data gaps in the existing methods and make recommendations for further development of methods/endpoints to assess OxS. New AOPs and methods could be developed in support of the Chemicals Sustainability Strategy (CSS) and in collaboration with the PARC consortium. T3.5 Identify candidates for training courses on the above-mentioned issues; STSM and ITC Conference Grants to stimulate them to apply for support.

Deliverables: D3.1 Methods and models used to assess oxidative status in humans, animals, and ecosystems, D3.2 WG meetings, D3.3 Training schools, D3.4 STSMs, D3.5 Reports on achievements D3.6 Report the identified gaps and recommendations.

WG4: Comparison of the role of OxS in AOPs in toxicology and ecotoxicology, its relevance of OxS-specific AOP key events in epidemiological studies and in the context of exposure to pesticide mixtures, implementation of OxS protocols. This WG aims at reaching the RCO4, RCO7, thanks to close and concerted exchanges between toxicologists and ecotoxicologists through the various above WG1 and 2 tasks. This WG involves biological, predictive, and modelling sciences.

Tasks will mainly consist of meeting, brainstorming and outreach activities and they will be shared into 4 subgroups to answer the questions below. A plenary meeting will be organized to collect the conclusions, perspectives and in particular the further needs (experimental designs to fill the identified gaps) and recommendations. The specific questions are:

T4.1 Could OxS-specific AOP key events be used as biomarkers of pesticide impact in toxicology and ecotoxicology?

T4.2 Could OxS-related endpoints in ecotoxicological assays be used as an indicator of adverse effects on human health?

T4.3 What is the relevance of OxS-specific AOP key events in epidemiological studies?

T4.4 How to integrate the OxS-specific AOP key events in the context of exposure to pesticide mixtures?

Deliverables: D4.1 Report on the results of the identification of specific OxS biomarkers related to pesticide- induced OxS relevant for both humans and the ecosystem, D4.2 WG meetings, D4.3 Training schools, D4.4 STSMs, D4.5 Reports on achievements, D4.6 Report on the identification of OxS-specific key events that could be considered biomarkers of the impact of pesticides in toxicology and ecotoxicology.

WG5: Giving input to regulatory agencies and industry for pesticide registration processes in Europe, dissemination of the acquired scientific knowledge. This WG aims at reaching the RCO8 & RCO9, with a better understanding of scientific possibilities regarding AOPs and their regulatory applications.

Tasks will include:
T5.1 A "Partner forum” with stakeholders from industry, and regulatory agencies or other partners, working in regulation, risk assessment or risk management for sharing knowledge and adopt recommendations. T5.2 Produce webinars with key experts to provide information relevant to European regulatory agencies about interest of the use of AOP and new database on pesticides and OxS in regulation process of pesticides (active substances and cocktail). D5.1 Evidence to support specific endpoints related to OxS in ecotoxicological assays that could be used as an indicator of human adverse effects, D5.2 Report on the transposition and/or relevance in epidemiological studies and integration of the endpoints identified in WG1 and WG2 in the context of exposures to low doses of pesticides mixtures, D5.3 Database specification and knowledge extraction protocol to correlate different MoAs and putative AOPs linking pesticide-induced OxS to several pathologies, D5.4 Exchanges with PARC on the development of new AOPs and methods in support of the CSS, D5.5 Sharing and dissemination of knowledge among researchers and students from different fields D5.6. Input about (eco)toxicity to regulatory agencies, industry and policy makers for pesticide registration processes in Europe as AOPs facilitate the compilation of information to increase mechanistic understanding of pathophysiological pathways (webinar), D5.7 Review redaction on the topic.
WG6: Communicating with public, professional users, occupational physicians, preventionists & healthcare professionals. This WG aims at reaching the RCO9. **Tasks** will include:
T6.1 Dissemination of scientific knowledge about pesticides (eco)toxicity to the society: professional users, and occupational physicians, preventionists & healthcare professionals, public.
D6.1 Technical journals, webinars to professional users, occupational physicians & healthcare professionals and preventers D6.2 Conferences, webinars, videos to the public.

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

The deliverables are detailed above (see 4.1.1) with the WG, tasks and activities.

Working Groups	Deliverables	Timeframe (M Month)	Working Groups	Deliverables	Timeframe (M Month)
WG1 & WG2	**D1.1, D1.3** **D1.2 & D2.2** **D1.4 & D2.4** **D1.5 & D2.5, D1.6 & D2.6,** **D1.7 & D2.7** **D1.8** **D1.9** **D1.10, D1.11**	**M6** **See Gantt chart** **M15** **See Gantt chart M24** **M27 M48** **See Gantt chart**	WG3	**D3.1** **D3.2, D3.3, D3.4, D3.5** **D3.6**	**M24** **See Gantt chart** **M42-M48**
WG4	**D4.1** **D4.2, D4.3, D4.4, D4.5** **D4.6**	**M36** **See Gantt chart M39**	WG5	**D5.1** **D5.2** **D5.3** **D5.4** **D5.5, D5.6, D5.7**	**M42 M45** **M48 M48** **M42-M45**
WG6	**D6.1 & D6.2**	**M24, M36, M45-48**			

4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

Scientific and technical risks

- To manage the risk of identifying a limited number of OxS-specific biomarkers based solely on AOPs, a literature analysis will be conducted with stakeholders leveraging complementary expertise.
- While synergy can arise when different disciplines collaborate, there is also a risk of miscommunication; thus, attention will be given to communication and culture during the Action. Many partners; especially the main proposer, have experience with multidisciplinary projects of COST Action and European project, as WG and/or WP leader. These multidisciplinary projects have been very successful in terms of valorisation (publications, international recommendations) and other outputs.
- Management risks will be warranted by the MC, comprising the Chair, Vice Chair, WG leaders and vice leaders, a science and communication manager, and STSM and training coordinator. Risk management will be a continuous process led by the Chair and the MC, and risks will be systematically identified at each WG meeting and temperance measures introduced.

4.1.4. GANTT DIAGRAM

Working Groups	Tasks	Year 1				Year 2				Year 3				Year 4			
		3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48
WGs 1 and 2	T1.1 & T2.1																
	T1.2 & T2.2																
	T1.3 & T2.3																
	T1.4																
	T1.5																
WG3	T3.1																
	T3.2																
	T3.3																
	T3.4																
	T3.5																
WG4	T4.1																
	T4.2																
	T4.3																
	T4.4																
WG5	T5.1 & T5.2																
WG6	T6.1																
	Activities																
	Kick-off meeting	x															
	WG meetings	x				x				x				x			x
	Website creation	x	x														
	Training or technical schools		x		x			x			x			x			x
	STSM		x			x					x				x		x
	Plenary meeting						x				x		x				x
	Reports on achievements				x				x					x			x
	Communication/workshops		x					x	x				x			x	x
	Valorisation							x				x					x

REFERENCES

1. Sharifi-Rad M. et al., Front Physiol. 2020; doi:10.3389/fphys.2020.00694.
2. Changwon Y. et al., Comparative Biochemistry and Physiology Part C: Toxicology & pharmacology, 2020:234; doi:10.1016/j.cbpc.2020.108758.
3. Valavanidis A. et al., Ecotoxicity and Environmental Safety 2006:64(2); doi:10.1016/j.ecoenv.2005.03.013.
4. Spaas J. et al., Cell Mol Life Sci. 2021:78(10); doi:10.1007/s00018-021-03802-0.
5. Singh A. et al., Molecules. 2019:24(8); doi:0.3390/molecules24081583.
6. Rajagopal V. et al., The Journal of Nutrition, 2021; doi:10.1093/jn/nxab309.
7. Mardinoglu A. et al., Cell Metab. 2018:27(3); doi:10.1016/j.cmet.2018.01.005.
8. Ankley G.T. et al., Environmental Toxicology and Chemistry, 2009:29; doi:10.1002/etc.34.
9. Bal-Price A. et al., Pharmacology & Therapeutics, 2017:179; doi:10.1016/j.pharmthera.2017.05.006.
10. Daniel L. et al., Toxicological Sciences, 2014:142(2); doi:10.1093/toxsci/kfu199.
11. Debost-Legrand A. et al., Environ Res. 2016 146:207-17; doi:10.1016/j.envres.2016.01.005
12. Pinos H, et al., Int J Environ Res Public Health. 2021:18(13); doi:10.3390/ijerph18137170.
13. Baudry J. et al., JAMA Int. Med. 2018:178; doi:10.1001/jamainternmed.2018.4357.
14. Rebouillat J. et al., Environ Health 2022:21; doi:10.1186/s12940-022-00862-y
15. Schäfer R.B. Current Opinion in Environmental Science & Health, 2019:11; doi:10.1016/j.coesh.2019.06.001.
16. Simbula G. et al., Ecotoxicology 2021:30; doi:10.1007/s10646-021-02440-3.
17. Radovanović, T.B. et al., Environ Toxicol Chem, 2017:36; doi:10.1002/etc.3849.
18. Teixeira H. et al., Science of The Total Environment, 2019:657, doi:10.1016/j.scitotenv.2018.11.440.
19. Lu T. et al., Microbiome. 2019:7(1); doi: 10.1186/s40168-019-0744-0.
20. Topaz T et al., Environ Pollut. 2020:265(Pt B); doi:0.1016/j.envpol.2020.114941.
21. Abdollahi M et al., Med Sci Monit. 2004:10(6) PMID: 15173684;
22. Zheng F et al., Redox Biology,2020:34; doi:10.1016/j.redox.2020.101475
23. Duarte-Hospital et al., Cells, 2021:11(1); doi:10.3390/cells11010110.
24. Semren T.Z. et al., Archives of Industrial Hygiene and Toxicology, 2018:69(2); doi:10.2478/aiht-2018-69-3118.
25. Deidda I. et al., Biology 2021:10; doi:10.3390/biology10020161
26. Lushchak V.I., Fish Physiol Biochem 2016:42; doi:10.1007/s10695-015-0171-5.
27. Pons DG, et al. Arch Insect Biochem Physiol. 2023 doi: 10.1002/arch.22028.
28. Biomarkers Definitions Working Group Clinical Pharmacology and Therapeutics, 2001:69, 89-95.
29. Pastore A. et al., Curr Drug Metab. 2015:16(1); doi:10.2174/138920021601150702161250.
30. Ledda, C. et al., J Occup Med Toxicol. 2021:16(1); doi:10.1186/s12995-020-00290-z
31. Costa C. et al., Int J Mol Med. 2020:45(6); doi:10.3892/ijmm.2020.4541.
32. Yang C. et al., Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology, 2020:234, doi:10.1016/j.cbpc.2020.108758.
33. Pikula K.S. et al., Current Opinion in Toxicology, 2019:13; doi:10.1016/j.cotox.2018.12.006.
34. Silvestre F., J Exp Zool A Ecol Integr Physiol. 2020:333(6); doi:10.1002/jez.2356.
35. He F. et al., Int J Mol Sci. 2020:21(13); doi:10.3390/ijms21134777
36. Liang X. et al., Comparative Biochemistry and Physiology Part D: Genomics and Proteomics, 2020:36; doi:10.1016/j.cbd.2020.100751.
37. Brockmeier E.K., Toxicol Sci. 2017:58(2); doi:10.1093/toxsci/kfx097.
38. Takano, H.K. et al., Photosynth Res 2020:144; doi:10.1007/s11120-020-00749-4
39. Wilkinson M. et al., Sci Data 2016:3(160018); doi:10.1038/sdata.2016.18
40. Martens, M. et al., Applied In Vitro Toxicology 2022: 8(1), 2-13; doi:10.1089/aivt.2021.0010
41. Delmas, M., et al., Bioinformatics 2021:37(21), 3896-3904.; doi: 10.1093/bioinformatics/btab627
42. Santovito G. et al., Comp Biochem Physiol C Toxicol Pharmacol. 2005:140(3-4); doi:10.1016/j.cca.2005.02.015.
43. Regoli S. et al., Environmental Research 2002:54(3-5); doi:10.1016/S0141-1136(02)00146-0
44. Williams A.J., et al., Environment international. 2021:154(106566); doi:10.1016/j.envint.2021.106566.
45. Lukowicz C. et al., Environ Health Perspect. 2018:126(6); doi:10.1289/EHP2877.
46. Schumann P. et al., Science of The Total Environment. 2024:912 doi:10.1016/j.scitotenv.2023.168573
47. Dufourcq-Sekatcheff E. et al., Env Toxicol Chem. 2024 Jul 9 doi:10.1002/etc.5940
48. The US EPA SeqAPASS v6.1; https://seqapass.epa.gov/seqapass/
49. Rivetti, C. et al., Environmental Toxicology and Chemistry. 2023:42(5) doi:10.1002/etc.5600