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INVESTIGATING NEUROTOXICITY DUE TO PESTICIDE RESIDUES IN THE FOOD CHAIN

MARIA D.K. DISERI

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Investigating Neurotoxicity due to Pesticide Residues in the Food Chain

MASTER'S DISSERTATION COMMITTEE:

Associate Professor Dimosthenis A. Sarigiannis
Director, Technologies Division,
Environmental Engineering Laboratory
Department of Chemical Engineering
Aristotle University of Thessaloniki, Greece

Dr Spyros Karakitsios
Environmental Health Researcher
Head of Exposure Biology Unit
Department of Chemical Engineering
Aristotle University of Thessaloniki, Greece

Professor Aristides M. Tsatsakis
Professor of Toxicology
Director of the Laboratory of Forensic Science & Toxicology
Medical School, University of Crete, Heraklion, Greece

DEDICATION

This dissertation is dedicated to my lovely parents for all their love and support and putting me through the best education possible. I appreciate their sacrifices since I would not be able to get to this level without them.

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ABSTRACT

In everyday life, humans may be exposed to chemicals at different occasions and in a number of different ways. Chemicals may be released into the environment during production or disposal of products and disperse into air, surface water or groundwater, soil, crops and wildlife. Occupational exposure to chemicals may also occur during production or use of a product. Furthermore, chemical exposure may result from the use of a large variety of consumer products. Finally, a large number of chemicals are deliberately used for specific applications (pesticides, biocides, veterinary products, food additives), resulting in exposure through food and other routes.

Regarding Pesticides or Plant Protection Products (PPRs), these have been used to protect crops from being damaged or destroyed by disease and pests and thus, to maintain crop yields since last century.

The majority of pesticides are chemicals. Residues are the measurable amounts of these chemicals resulting from the use of pesticides that remain on cereals, fruit and vegetables after harvesting. Pesticides residues present on crops used to feed animals and in the environment can be found in foods of animal origin such as meat, milk and eggs.

By their nature, pesticides are potentially toxic to other organisms, including humans, and need to be used safely and disposed of properly. The EU approach to pesticides aims to pesticide use be limiting to the minimum quantity that allows them to carry out their job effectively while ensuring food is safe to eat. Thus, the pesticide residues in food and feed are being monitored on each Member State (MS) annually. These results are included in the annual report by EFSA (European Food Safety Authority) which additionally, assesses the exposure of EU – consumers to these residues. As EU decision – makers use these data as a basis for future actions such as monitoring activities, pesticide authorisations and MRL setting, this has resulted in the removal of the EU-market of a large number of pesticides that failed to meet current safety standards.

Methods: The present study is focused on examining the safety approach of pesticide residues found in various food categories together with their potential cumulative effect. This study is based on data from EFSA regarding the dietary consumption of consumers in the country of Greece whereas, the diet survey was addressed to “lactating diet” on the one hand and “regional Crete” on the other hand.

The population class chosen was “lactating women” and “children”, respectively. The values of pesticide residues present in various food categories were extracted from many studies involving mostly European markets and less international ones.

Results: It is discussed the evidence for possible contributions of environmental chemicals to Neurotoxicity including Developmental Neurotoxicity (DNT) and Cancer risk, as end-points. Therefore, the outcome of Risk Characterisation Ratio (RCR) for Chronic and Acute exposure, Margin of Safety (MoS), Cumulative Chronic risk and Cumulative Cancer risk has been assessed.

Conclusions: Acute risk to human health has been induced by the presence of some pesticide residues in foods for the sub – population “lactating women”. The most important aspect of this study is the identification of cumulative cancer risk to both sub – populations “**lactating women in Greece**” and “**children in the regional prefecture of Crete**” due to the consumption of foods detected with various pesticide residues. According to the latest scientific development internationally that gave rise to cumulative risk assessment, cumulative effects will only occur when chemicals with similar toxicological properties present on food are consumed together. Thus, the development of pesticides with better qualitative and quantitative attributes with regard to elimination of severe toxicity effects to human health should be progressed and also combined with effective pest management training to all stakeholders.

1. INTRODUCTION

1.1. PESTICIDES

1.1.1. TERMS – DEFINITIONS – CLASSES

According to the website of the Directorate General for Health and Food Safety of the European Commission, the term **"pesticide"** is referred to as "**something that prevents, destroys, or controls a harmful organism ("pest") or disease, or protects plants or plant products during production, storage and transport**".

The term includes, amongst others: herbicides, fungicides, insecticides, acaricides, nematicides, molluscicides, rodenticides, growth regulators, repellents and biocides.[1]

According to EFSA (European Food Safety Authority) website, the term "pesticides" is commonly used as a synonym for plant protection products. **Plant protection products (PPPs)** are pesticides that are mainly used to keep crops healthy and prevent them from being destroyed by disease and infestation. They include herbicides, fungicides, insecticides, acaricides, plant growth regulators and repellents.[2]

Plant protection products contain at least one **active substance**. These substances can be chemicals or micro-organisms, including viruses that enable the product to perform its action. In the current study, whenever the term "pesticides" is used this refers to the plant protection products and the active substances contained in them.

PPPs are products in the form in which they are supplied to the user, consisting of, or containing active substances, safeners or synergists, and intended for one of the following uses[3]:

- (a) protecting plants or plant products against all harmful organisms or preventing the action of such organisms, unless the main purpose of these products is considered to be for reasons of hygiene rather than for the protection of plants or plant products (e.g. fungicides, insecticides);
- (b) influencing the life processes of plants, such as substances influencing their growth, other than as a nutrient (e.g. plant growth regulators, rooting hormones);

- (c) preserving plant products, in so far as such substances or products are not subject to special Community provisions on preservatives (e.g. extending the life of cut flowers);
- (d) destroying undesired plants or parts of plants, except algae unless the products are applied on soil or water to protect plants (e.g. herbicides/weedkillers to kill actively growing weeds);
- (e) checking or preventing undesired growth of plants, except algae unless the products are applied on soil or water to protect plants (e.g. herbicides/weedkillers preventing the growth of weeds).

The pesticides are classified under functional **classes**, according to the Codex Alimentarius, as follows[19]:

- **Acaricide**
- **Aphicide**
- **Fumigant**
- **Fungicide**
- **Generic**
- **Herbicide**
- **Insect growth regulator**
- **Insecticide**
- **Nematocide**
- **Plant growth regulator**
- **Scald control agent**
- **Storage scald preventer**
- **Synergist**

1.1.2. PESTICIDES AND EU – LEGISLATION

The **placing of a pesticide on the EU market** is regulated by the "**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".[3] At this point, it is necessary to present the following definitions that apply under this Regulation:

"**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.

“**Substances**” means chemical elements and their compounds, as they occur naturally or by manufacture, including any impurity inevitably resulting from the manufacturing process.

“**Substance of concern**” means any substance which has an inherent capacity to cause an adverse effect on humans, animals or the environment and is present or is produced in a plant protection product in sufficient concentration to present risks of such an effect. Such substances include, but are not limited to, substances meeting the criteria to be classified as hazardous in accordance with 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, and present in the plant protection product at a concentration leading the product to be regarded as dangerous within the meaning of Article 3 of Directive 1999/45/EC.

“**Plant products**” means products of plant origin in an unprocessed state or having undergone only simple preparation, such as milling, drying or pressing, but excluding plants.

“**Harmful organisms**” means any species, strain or biotype belonging to the animal kingdom or plant kingdom or pathogenic agent injurious to plants or plant products.

“**Non-chemical methods**” means alternative methods to chemical pesticides for plant protection and pest management, based on agronomic techniques such as those referred to in point 1 of Annex III to Directive 2009/128/EC, or physical, mechanical or biological pest control methods.

“**Authorisation of a plant protection product**” means an administrative act by which the competent authority of a Member State authorises the placing on the market of a plant protection product in its territory.

“**Rapporteur Member State (RMS)**” means the Member State which undertakes the task of evaluating an active substance, safener or synergist.

All matters related to legal limits for pesticide residues in food and feed are covered by Regulation (EC) No 396/2005.[7] This regulation also contains provisions on official controls of pesticides residues in food of plant and animal origin that may arise from their use in plant protection.

The residues of the plant protection products, consequent on application consistent with good plant protection practice and having regard to realistic conditions of use, shall meet the following requirements: (a) they shall not have any harmful effects on human health, including that of vulnerable groups, or animal health, taking into account known cumulative and synergistic effects where the scientific methods accepted by the Authority to assess such effects are available, or on groundwater; (b) they shall not have any unacceptable effect on the environment.[3]

For residues which are of toxicological, ecotoxicological, environmental or drinking water relevance, there shall be methods in general use for measuring them. Analytical standards shall be commonly available.[3]

1.1.3. SUSTAINABLE USE OF PESTICIDES

The EU sets rules for the sustainable use of pesticides to reduce the risks and impacts of pesticide use on people's health and the environment (Directive 2009/128/EC).[4]
Main Actions for sustainable use of pesticides:

- **National Action Plans** – EU countries adopt them setting objectives and timetables to reduce risks and impacts of pesticide use.
- **Training** – Professional pesticide users, distributors and advisors get proper training.
  EU countries establish competent authorities and certification systems.
- **Information and awareness raising** – Member States shall take measures to inform the general public and put in place systems to gather information on acute poisoning incidents and chronic poisoning developments.
- **Aerial spraying** – Aerial spraying is prohibited. EU countries may allow it under strict conditions after warning people.
- **Minimising or banning** – EU countries minimise or ban the use of pesticides in critical areas for environmental and health reasons.
- **Inspection of equipment in use** – All pesticides application equipment will have to be inspected at least once by 2016 to grant a proper efficient use of any plant protection product;
- **Integrated pest management (IPM)** – Promotion of low pesticide-input management including non-chemical methods. Professional users will have to apply general principles of IPM from 1 January 2014.[5]

1.1.4. APPROVAL OF ACTIVE SUBSTANCES

A plant protection product usually contains more than one component. The active component against pests /plant diseases, as mentioned above, is called “active substance”. The Commission evaluates every active substance for safety before it reaches the market in a product. Substances must be proven safe for people's health, including their residues in food and effects on animal health and the environment.

Procedure:

1. Application to an EU country called *Rapporteur Member State (RMS)*
2. RMS verifies if the application is admissible
3. RMS prepares a draft assessment report
4. EFSA issues its conclusions
5. Standing Committee for Food Chain and Animal Health votes on approval or non-approval
6. Adoption by the Commission
7. Publication of a Regulation in the EU Official Journal

Under the new EU rules, it takes **2.5 to 3.5** years from the date of admissibility of the application to the publication of a Regulation approving a new active substance. This time varies greatly as depends on how complex and complete the dossier is.[6]

Before an active substance can be used within a pesticide in the EU, it must be **approved** by the European Commission.

Substances undergo an intensive evaluation and peer-review by Member States and the European Food Safety Authority before a decision can be made on approval.

1.1.4.1. LIST OF CANDIDATES FOR SUBSTITUTION

“The European Commission is required by Regulation (EC) No 1107/2009 to establish a list of substances identified as “candidates for substitution”. The list identifies **active substances with certain properties**.

For plant protection products (PPPs) containing these active substances, Member States will be required to evaluate if they can be replaced (substituted) by other

adequate solutions (chemical and non-chemical). To prepare such a list, the Commission requested a consultant to prepare a **report** on the implementation of the criteria set by the Regulation. The report **does not contain any official listing**, but presents **different options** drawn from possible interpretations of the criteria.

Member States and stakeholders were consulted on the approach taken and on the input values taken to determine if an active substance qualifies to be a candidate for substitution. The analysis has been conducted by comparing the agreed and peer reviewed endpoints, against the relevant seven conditions specified in Annex II, point 4 of the Regulation. The information is grouped in a **comprehensive database** that will be updated on a regular basis. The current draft list contains **77 candidates for substitution**.[6]

1.1.5. AUTHORISATION OF PESTICIDES

According to a large body of EU legislation, the release of a plant protection product into the market is divided into two major parts that are in close collaboration; the one is undertaken by EFSA through evaluation of the active substances based on their risk assessment and the other, by the Member States that evaluate and authorise the products at national level.[2]

EU countries authorise pesticides on their territory and ensure compliance with EU rules. Regulation (EC) No 1107/2009 lays down the rules, procedures and timeframes for authorisation of PPPs. Prior to placing on the market or using any pesticide, it must be authorised in the Member State(s) concerned.

The application procedure is dependent on a zonal system in EU to enable a harmonised and efficient system to operate. The EU is divided into 3 zones; North, Central and South. Member States assess applications on behalf of other countries in their zone and sometimes on behalf of all zones. Applicants, Member States, the European Commission and the European Food Safety Authority (EFSA) can be involved in the process of authorisation.[8]

There are different types of application that can be submitted depending on the intended use of the PPP, the Member State(s) for which the PPP is required and the regulatory status of any existing authorisations. The controls of the use and placing on the market of PPPs are performed by Member States.[8]

1.1.6. MAXIMUM RESIDUE LEVEL (MRL)

In simple words, the traces a pesticide leaves in treated products is called “residue”. Pesticide residues resulting from the use of plant protection products on food or feed crops may pose a risk to public health. For this reason, a comprehensive legislative framework has been established in the European Union which defines rules for the approval of active substances used in plant protection products, the use of plant protection products and for pesticide residues in food.

Maximum residue levels (MRLs) are the upper levels of pesticide residues that are legally permissible in or on food or animal feed, based on good agricultural practice (GAP) and the lowest consumer exposure necessary to protect vulnerable consumers. They are derived after a comprehensive assessment of the properties of the active substance and the intended use of the pesticide. These legal limits also apply to imported food.[2]

Before an MRL is set or amended – for example, because an applicant requests the authorisation of a new plant protection product – **EFSA** assesses the residue behaviour of the pesticide and possible consumer health risks from residues in food. Provided that EFSA’s risk assessment does not identify any unacceptable risks to consumers, EU-harmonised MRLs are set (**Database of MRLs in the EU**) [9] and the plant protection product can be authorised. As well as assessing new MRLs, the Pesticides Unit, in close cooperation with Member States, reviews the scientific basis of existing MRLs and performs **consumer risk assessments** to ensure they are compliant with current data requirements and are safe for consumers. The outcome of EFSA’s MRL assessments are presented as **reasoned opinions**.[2]

Chronic (long-term) and acute (short-term) dietary consumer exposure to pesticide residues are estimated using a **calculation model** developed by **EFSA** (**PRIMo – Pesticide Residue Intake Model**) [10]. The model is based on national food consumption data and unit weights provided by Member States and implements internationally agreed risk assessment methodologies.[2]

All the above process – from approval of active substances to authorisation of PPPs – contributes to better protection of agricultural production and at the same time is ensuring that PPPs, when properly applied for the purpose intended, are sufficiently

effective and have no unacceptable effects on plants and plant products, on the environment and there are no harmful effects on humans. Despite this rather strict and costly pre-market pesticide approval process, pesticides and their conversion products end up in the plants and plant products in undesirable concentrations posing toxicological risk to various population categories.

1.1.7. PESTICIDES AND HUMAN HEALTH – NEUROTOXICITY

Pesticides are one of the most commonly encountered classes of neurotoxic substances. They can include insecticides (used to control insects), fungicides (i.e. for blight and mildew), rodenticides (for rodents, such as rats, mice and gophers) and herbicides (to control weeds) (Hayes, 1991).[28] Active ingredients are combined with so-called inert substances to make thousands of different pesticide formulations. Workers who are overexposed to organophosphate pesticides may display obvious signs and symptoms of poisoning, including tremors, weakness, ataxia, visual disturbances and short-term memory loss (Ecobichon J. & Joy M., 1982; Abou-Donia M.B., 1995).[29, 30]

The organophosphate insecticides have neurotoxic properties and account for approximately 40% of registered pesticides in the USA. Delayed neurotoxicity can be seen as a result of exposure to certain organophosphate pesticides, producing loss of motor function and an associated neuropathology (Ecobichon D.J. & Joy R.M., 1982).[29]

Organophosphate and carbamate insecticides are known to interfere with a specific enzyme, acetylcholinesterase (AChE) (Davis C.S. & Richardson R.J., 1980; Abou-Donia M.B., 1995; Metcalf R.L., 1995).[30,31,32] Neuropathy has also been reported following consumption of non-pesticide organophosphates, such as tri-*o*-cresylphosphate (TOCP).

Other classes of pesticides, including the organochlorines (Cannon et al., 1978; Woolley D.E., 1995)[33, 34] and pyrethroids (Clark J.M., 1995)[35], may produce signs of functional neurotoxicity. A number of reports have noted that many cases of human poisonings due to the ingestion or absorption of neurotoxic pesticides go unreported. This is especially true in developing countries, where up to 45% of pesticide poisoning cases occur in young children (WHO, 2000).[36]

Structure-activity relationships (SARs) are widely used to predict toxicological properties of chemicals based on chemical structure. The basis for inference from SARs can be either comparison with structures known to have biological activity or knowledge of structural requirements of a receptor or macromolecular site of action. Although information from SARs can significantly aid in the design of studies, there have been limitations. In neurotoxicology, as in many other areas, there have been relatively few well characterized SARs. However, there are some examples where SARs have been demonstrated and have provided guidance for evaluating additional compounds such as, organophosphorus compounds predicted to cause organophosphate-induced delayed neurotoxicity (Johnson M.K., 1988).[17, 26]

To date, SARs have been demonstrated only for some specific forms of neurotoxicity; thus, the use of SARs for excluding potential neurotoxicity is not generally acceptable. For some homologous groups of chemicals, SARs combined with knowledge of chemical or physical properties have provided information on the risk of acute neurotoxicity or narcotic effects.[17]

Such information is helpful for evaluating potential toxicity when only minimal data are available. The SARs of some chemical classes, such as hexanes, organophosphates, carbamates and pyrethroids, may help predict neurotoxicity or interpret data from neurotoxicological studies. Under certain circumstances (e.g., in the case of new chemicals), this procedure is one of the primary methods used to evaluate the potential for toxicity when few or no empirical toxicity data are available. It should be recognized, however, that effects of chemicals in the same class can vary widely. Moser (1995)[27], for example, reported that the behavioural effects of prototypic cholinesterase-inhibiting pesticides differed qualitatively in a battery of behavioural tests.[17]

1.2. NEUROTOXICITY

1.2.1. DEFINITIONS

Neurotoxicity occurs when the exposure to natural or manmade toxic substances (neurotoxicants) alters the normal activity of the nervous system. This can eventually disrupt or even kill neurons, key cells that transmit and process signals in the brain and other parts of the nervous system. Neurotoxicity can result from exposure to substances used in chemotherapy, radiation treatment, drug therapies, and organ

transplants, as well as exposure to heavy metals such as lead and mercury, certain foods and food additives, pesticides, industrial and/or cleaning solvents, cosmetics, and some naturally occurring substances. Symptoms may appear immediately after exposure or be delayed. They may include limb weakness or numbness; loss of memory, vision, and/or intellect; headache; cognitive and behavioral problems; and sexual dysfunction. Individuals with certain disorders may be especially vulnerable to neurotoxicants.[11]

1.2.2. THE NERVOUS SYSTEM

The nervous system receives and sends signals throughout the body to control bodily functions. The nervous system consists of the central nervous system (brain and spinal cord) and peripheral nervous system (nerve fibers that attach to and lie outside the brain and spinal cord). The nervous system has two components, motor (efferent) and sensory (afferent), that carry information from and to, respectively, the central nervous system. The brain is the organ of thought, emotion, and processing of the various senses and communicates with and controls various other systems and functions. The nervous system also provides special senses such as sight, hearing, taste, feel, and smell. It uses the eyes, ears, tongue, skin, and nose to gather information about the body's environment.[18]

According to the International Programme on Chemical Safety (IPCS) – Environmental Health Criteria 60, the importance of studying the Nervous System lays down to its complexity. The brain is an extremely complex organ, the function of which is to receive and integrate signals and then to respond appropriately, to maintain bodily functions. It supports a diversity of complex processes including cognition, awareness, memory, and language. Sexual behaviour, locomotion, and the use of a vast array of tools ranging from the slingshot to the microcomputer, suggest the range of responses available to the human organism. Moreover, the nervous system is influenced by the functioning of other organ systems (e.g., hepatic, cardiovascular, and endocrine systems). Thus, toxicant-induced alterations in any of these organ systems can be reflected in changes in neurobehavioural output. This fact alone suggests that nervous system function should be among the first to be thoroughly assessed in cases of exposure to known or potentially hazardous agents. Major outbreaks of neurotoxicity in human populations of various sizes have emphasized the importance of neurotoxicology as an independent discipline.[12]

The science of Neurotoxicology includes studies on the actions of chemical, biological, and certain physical agents that produce adverse effects on the nervous system and /or behaviour during development and at maturity. Toxic disorders of the nervous system of human beings and animals may occur following abuse of such substances as ethanol, inhalants, narcotics, therapeutic drugs, products or components of living organisms (e.g., bacteria, fungi, plants, animals), chemicals designed to affect certain organisms (e.g., pesticides), industrial chemicals, chemical warfare agents, additives and natural components of food, raw materials for perfumes, and certain other types of chemicals encountered in the environment.[12]

Caution must be exercised in labelling a substance neurotoxic. The intended use and effect of the compound, the dose, the exposure scenario and whether or not the compound acts directly or indirectly on the nervous system must be taken into consideration. For example, pharmaceutical agents, vitamins and herbal substances may offer safe and beneficial effects at low concentrations, whereas higher doses may result in neurotoxicity. Therefore, the neurotoxic potential always needs to be considered in terms of the dose relationship.[17]

1.2.3. METHODS FOR ASSESSING HUMAN NEUROTOXICITY

1.2.3.1. CLINICAL NEUROLOGICAL EVALUATION

The assessment of potential neurotoxicity in individuals begins with a clinical evaluation of an individual patient in order to establish a differential diagnosis of neurotoxic disease and to rule out other possible etiologies. The clinical evaluation of a suspected case of neurotoxicity includes a detailed medical history and a standard clinical neurological examination. Depending on the clinical signs, symptoms or type of exposure, these techniques may be supplemented by other assessment procedures, including clinical neuropsychological evaluation, neurophysiological tests and neuroimaging techniques.[17]

1.2.3.2. NEUROPSYCHOLOGICAL AND NEUROBEHAVIOURAL TESTING

1.2.3.2.1. INDIVIDUAL NEUROPSYCHOLOGICAL ASSESSMENT

In addition to the neurological examination, neuropsychological testing is often carried out in the clinical evaluation of neurotoxicity, especially in those cases where there is an indication of cognitive or affective changes. Similar to the neurological

examination, neuropsychological testing also helps in ruling out other etiologies as well as establishing the extent of psychological impairment.[17]

1.2.3.2.2. COGNITIVE TESTING BATTERIES

One approach to evaluating changes in neurobehavioural functioning in studies of exposed populations involves a shortened battery of clinical neuropsychological tests that focus on those effects most commonly seen in CNS toxic disorders.[17]

1.2.3.2.3. PSYCHIATRIC AND SYMPTOM QUESTIONNAIRES

Changes in affect are some of the most dramatic effects of severe neurotoxic exposures. Psychotic symptoms, including delusions, hallucinations and paranoia, have been noted in mercury, arsenic and manganese poisoning cases (White R.F. & Proctor S.P., 1995)[37], and suicidal depression resulting from poisoning with carbon disulfide has been well known for over a century (Mikkelsen S., 1995).[38] Less severe effects (e.g., changes in mood and energy levels) have also been reported in exposed populations and, in some cases, may be the earliest indication of neurotoxic exposure (IPCS, 1986).[12] As a result, questionnaires and symptom ratings are also typically included both in the assessment of individual neurotoxicity cases and in epidemiological studies of exposed populations.[17]

1.2.3.2.4. BEHAVIOURAL NEUROPHYSIOLOGICAL TESTS

Because sensory and motor changes have often been associated with exposure to particular chemicals, both the neurological examination and symptom questionnaires typically include items designed to obtain information regarding sensory and motor disturbances. In recent years, although neurotoxic exposures have been associated with effects on different sensory modalities, including hearing, most of the work in the area of behavioural neurophysiological testing has concentrated on colour vision, contrast sensitivity, vibration sensitivity and olfactory discrimination.[17]

1.2.3.3. ELECTROPHYSIOLOGICAL TESTS

Similar to behavioural tests, electrophysiological tests of PNS and CNS function may be used to augment the neurological examination. Although these tests are not in themselves diagnostic of neurotoxicity, they can be used to help detect and characterize dysfunction. Electrophysiological methods are generally used to diagnose individual patients but could be applied to the study of exposed populations, particularly exposed workers. One advantage of electrophysiological

tests is that many techniques are directly applicable to animal studies, making possible direct cross-species comparisons.

Recent developments in quantitative neurophysiological methods provide promising research tools for the evaluation of neurotoxicity in humans. Popular techniques have included, peripheral nerve testing and SEPs, qEEG, the analysis of the P300 waveform and ERPs. However, further research aimed at standardizing techniques, validating different methodologies and examining the effects of different exposures is necessary before such methods can be accepted as diagnostic instruments.[17]

1.2.3.4. NEUROIMAGING TECHNIQUES

Over the last 20 years, a number of image-producing technologies, such as computerized axial tomography (CAT), magnetic resonance imaging (MRI), positron emission tomography (PET) and single photon emission computerized tomography (SPECT) have been developed for use in the diagnosis of neurological disease. CAT and MRI produce images of the brain, and PET and SPECT supply functional or biochemical information that cannot be obtained with other methods in a non-invasive manner. Neuroimaging techniques provide an invaluable measure of local brain function and dysfunction, which can be integrated with neurobehavioural measures for studying brain-behaviour relationships at the human level. Neuroimaging techniques provide a unique research tool with which to investigate structural and biochemical changes in neurotoxic disease and, in the future, may constitute an important source of information regarding structural and functional changes in the human brain as a function of neurotoxic exposures.[17]

In conclusion, there has been significant progress in the last decade in developing validated methods for detecting neurotoxicity in humans as well as an increased understanding of the factors that impact on the validity and reliability of human neurotoxicity studies. Standardised neuropsychological tests, validated computer-assisted test batteries, neurophysiological and biochemical tests, and refined imaging techniques have been improved for use in both clinical and research applications. These techniques are being utilized in different epidemiological study designs to examine the relationship between exposure to neurotoxic compounds and health effects.[17]

Since the determination of exposure-response/effect relationships is a prerequisite for inferring a causal relationship between a chemical and a health effect, reliable and valid methods to determine the degree of exposure are of critical importance in these studies. Environmental monitoring can be used to measure current levels of external exposure, and biochemical techniques can be used to measure levels of internal exposure. Modelling techniques, such as PBPK modelling, may also prove useful in helping to interpret biomonitoring data. These objective measures, coupled with subject-specific information, can be used to provide estimates of dose. Recent studies, however, demonstrate the difficulties in obtaining reliable estimates of exposure and dose in human studies and highlight the need for improved methods in this area. In addition, the development of methods for measuring early biochemical effects (i.e., biomarkers of effect), which could be used to monitor early, readily reversible effects, should also be encouraged.[17]

In addition, there are important individual differences in susceptibility to neurotoxic agents. The developing nervous system appears to be particularly vulnerable to some kinds of damage, and there is concern that neurotoxic exposure may be a contributory factor in neurodegenerative processes related to aging as well. Genetic differences in the metabolism of xenobiotics may also be of etiological importance in the expression of neurotoxic disease. Although progress has been made in the development of assessment techniques in children, more research is needed to establish normative data for use in different populations. Similarly, the study of the role of aging and genetic factors in the etiology of neurotoxic disease is also necessary.[17]

1.2.4. ANIMAL STUDIES – FACTORS TO BE CONSIDERED IN THE DESIGN OF NEUROTOXICITY

Determining the risk posed to human health from chemicals requires information about the potential toxicological hazards and the expected levels of exposure. Some toxicological data can be derived directly from humans. Sources of such information include accidental exposures to industrial chemicals, cases of food-related poisoning, epidemiological studies and clinical investigations. Although there are human data from clinical trials for drugs providing the most direct means of determining effects of potentially toxic substances, it is usually not applicable to other categories of substances. Quite often, the nature and extent of available human toxicological data are too incomplete to serve as the basis for an adequate assessment of potential

health hazards. Furthermore, for a majority of chemical substances, human toxicological data are simply not available.[17]

Consequently, for most toxicological assessments, it is necessary to rely on information derived from animal models, usually rats or mice. One of the primary functions of animal studies is to predict human toxicity prior to human exposure. In some cases, species phylogenetically more similar to humans, such as monkeys or baboons, are used in neurotoxicological studies.[17]

Biologically, animals resemble humans in many ways and can often serve as adequate models for toxicity studies (Russell, 1991).[25] This is particularly true with regard to the assessment of adverse effects on the nervous system, whereby animal models provide a variety of useful information that helps minimize exposure of humans to the risk of neurotoxicity. There are many approaches to testing for neurotoxicity, including whole-animal (in vivo) testing and tissue/cell culture (in vitro) testing.[17]

In using animal models to predict neurotoxic risk in humans, it is important to understand that the biochemical and physiological mechanisms that underlie human neurological and psychological functions are often incompletely understood and, therefore, are difficult, if not impossible, to model exactly in animals. While this caveat does not preclude extrapolating the results of animal studies to humans, it does highlight the importance of using valid animal models in well-designed experimental studies.[17]

1.2.4.1. GENERAL CONSIDERATIONS

Many factors must be taken into consideration with regard to any animal toxicology study. These include the choice and number of animals, dosage, route and duration of administration, metabolism and pharmacokinetics, and testing procedures.

1.2.4.2. OBJECTIVES

The nervous system is protected from undesirable external influences by both physical and chemical barriers. This protection, however, is not complete. The blood-brain barrier has an important function in preserving the chemical constitution of the nervous system, but some noxious substances, particularly those that are lipid soluble, may still cross it. Another mode of entry is by uptake into the peripheral terminals of nerves, which may then transfer the substances into their cell bodies in

the central nervous system through retrograde axonal flow. Such a mechanism operates for substances as remote as tetanus toxin and some viruses.[12]

The peripheral nervous system is, of course, more likely to be exposed to neurotoxicity. The neurons of the autonomic nervous system and the sensory ganglia are outside the blood-brain barrier, as are small regions of the CNS (Central Nervous System), circumventricular organs (e.g., area postrema) and, to a limited extent, the retina. As might be expected, the nervous system may be particularly vulnerable either during development or in senescence. Physical changes or the presence of toxins may also disrupt the blood-brain barrier and, thus, allow substances normally excluded from the brain to reach and affect it adversely.[12]

The objectives of neurotoxicity testing are to:

(a) **identify** whether the nervous system is altered by the toxicant (detection);

(b) **characterise** the nervous system alterations associated with exposure;

(c) **ascertain** whether the nervous system is the primary target for the chemical; and (d) determine dose– and time– effect relationships aimed at establishing a no-observed-adverse-effect level.

In a sense, these objectives translate into a series of questions about the toxicity of a chemical, and achieving them requires behavioural, neurophysiological, biochemical, and neuropathological information.[12]

When faced with a chemical for which no toxicological data are available, the first question is whether the nervous system is or is not affected by the chemical. This represents the most fundamental level of investigation and entails procedures that "screen" for neurotoxicity. Once a chemical is known to produce neurotoxic effects, further studies must be performed in order to characterize the nature and mechanism of the alterations. These studies explore the consequences of toxicant exposure and give an indication of whether or not the nervous system is the primary target organ. Many functions are mediated by unique neural substrates, and chemicals may produce selective effects. Thus, it is important to use a variety of tests that measure different functions, in order to maximize the probability of detecting a toxic effect.[12]

Although certain chemicals produce selective damage in the nervous system, a more common finding is one of widespread damage and disruption of a variety of functions. Ideally, characterization of such generalized neurotoxicity by a variety of methods will establish a profile of the disrupted functions.

Once a chemical has been identified as neurotoxic, the next objective is to determine dose-effect and time-effect relationships. One aim of these studies is to establish no-observed-adverse-effect levels, but to prove that a certain dose produces no effect may require a very large number of experimental animals (Dews P.B., 1982).[39] To be useful in risk assessment, threshold determinations must be obtained by the most sensitive tests available.[12]

The question of how to define toxicity is of critical importance for the ultimate goal of risk assessment and the establishment of hygienic standards. Considerable controversy exists concerning what constitutes an adverse effect in toxicology. According to one view, any evidence of a behavioural or biological change is considered to be an adverse effect. According to others, evidence is required of both an irreversible decrement in the ability of the organism to maintain homeostasis and/or an enhanced susceptibility to the deleterious effects of other environmental influences. In this latter view, differentiation between "non-adversive" and "adverse" effects requires considerable knowledge of the importance of reversible changes and subtle departures from "normal" behaviour, physiology, biochemistry, and morphology in terms of the organism's overall economy of life, ability to adapt to other stresses, and their possible effects on life span (WHO, 1978).[13] Real or potential risks to the nervous system are difficult to assess because of its complexity. Some of the problems in assessment are associated with the wide variations that can occur but are still considered to be within the "normal" range. Some are associated with the plasticity of the nervous system. Other problems in assessment are related to incomplete understanding of what is being measured by certain tests. It is clear, therefore, that no single test will suffice to examine the functional capacity of the nervous system. The above comments suggest tiered testing approaches.[12]

1.2.4.3. CHOICE OF ANIMALS

For obvious reasons of safety and ethics, it is necessary to use animals in toxicity assessments. However, the extrapolation of animal toxicological data to human beings is always tenuous and should be carried out with caution. In preliminary mass screening of known or suspected environmental toxicants, there are economic factors that must be taken into account. It is also important that there be adequate anatomical, physiological, pharmacological, and toxicological data bases on the species chosen for study, so that meaningful interpretations of effects can be made and appropriate hypotheses about mechanisms and loci of action can be framed.[12]

For these reasons, the mouse or rat is usually preferred in a preliminary screen, though the rodent differs from man in many significant ways. For more detailed studies, other species may provide a more appropriate model. For example, the adult chicken is the animal of choice to test organophosphate induced delayed neurotoxicity (Abou-Donia M.B., 1981).[14]

Other variables, besides species, that must also be considered such as, the strain of animal used, its age and of course, its sex (male, female).

1.2.4.4. DOSING REGIMEN

In environmental toxicology, the detection of cumulative toxicity following continued (or intermittent) exposure is a major goal. Thus, a **multiple-dosing regimen** is most frequently used. It is important to assess the toxicity at various intervals, since both quantitative and qualitative changes in the response to environmental factors can occur on repeated exposure, or even with time following a single exposure (Evans H.L. & Weiss B., 1978).[15] Assessments should be made for some time following cessation of the dosing regimen, since it is of interest to determine the reversibility of any effects noted during the dosing phase and to note any post-dosing effects.[12]

1.2.4.5. FUNCTIONAL RESERVE AND ADAPTATION

Functional reserve is the excess capacity possessed by the nervous system. Thus, a portion of the nervous system can be damaged, and this damage can go undetected by the usual functional tests. The situation in which a change in function was observed at one time, but can no longer be detected by the usual functional tests, is referred to as adaptation and presumably reflects compensatory processes.

If a part of a redundant system is damaged, it is reasonable to assume that the reserve potential has been reduced. If compensatory changes have occurred, the ability of a system to make further compensatory changes may also have been reduced. One way to assess such changes is to incorporate in the test procedures one or more conditions in which the system(s) or organism(s) are placed under stress. The combination of the test substance plus stress may result in a greater deficit in performance than can be seen in animals receiving either the stress or the toxicant only.[12]

1.2.4.6. OTHER FACTORS

Several additional factors should be carefully considered in designing neurotoxicological tests. One condition that may affect toxicity is the nutritional state of the animal. Changes attributed to exposure to toxicants might be due to relatively nonspecific effects related to inhibition of growth or decreases in food or water consumption. This is particularly true in studies involving developing organisms.

Another variable is the housing conditions of the experimental animal. In some cases, animals are housed individually in home cages during pharmacological or toxicological studies. This arrangement can alter the responsiveness of the subjects to drugs.

Moreover, it has been observed how biological rhythms influence the pharmacological and toxicological response to chemicals (Reiter L.W. & MacPhail R.C., 1982).[16] These biological rhythms cannot be ignored and must be either controlled for in the study or studied explicitly.[12]

1.3. NEUROTOXICITY RISK ASSESSMENT

1.3.1. RISK ASSESSMENT PRINCIPLES

Risk analysis is a process that incorporates three components: risk assessment, risk management and risk communication. The first component, risk assessment, consists of scientific analyses, the results of which are quantitative or qualitative expressions of the likelihood of harm associated with exposure to a chemical.[20]

The assessment of human health risk requires identification, compilation and integration of information on the health hazards of a chemical, human exposure to the chemical and relationships among exposure, dose and adverse effects. Acquisition of information appropriate to a scenario of interest is a fundamental challenge in risk assessment. Numerous sources of such information can be readily found through literature searches facilitated by electronic tools. Compilations of relevant data prepared by international and other organisations also provide rapid access to information on chemical hazards, exposures and risks.[20]

Risk assessment is a process intended to identify and then to calculate or estimate the risk for a given target system to be affected by a particular substance, taking into

account the inherent characteristics of the substance of concern as well as the characteristics of the specific target system.[17]

Risk management is a decision-making process involving considerations of political, social, economic and technical factors with relevant risk assessment information relating to a hazard so as to develop, analyse and compare regulatory and non-regulatory options and to select and implement the optimal response for safety from that hazard. Hazard refers to the inherent property of a substance capable of having adverse effects (OECD/IPCS, 2001).[40]

Throughout the document, frequent reference is made to some terms developed entirely from toxicological and epidemiological information, such as the acceptable daily intake (ADI) and acute reference dose (ARfD). Their definition is as follows:

"**acute reference dose (ARfD)**" 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 (24h or less), 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).[7]

"**acceptable daily intake (ADI)**" 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).[7]

1.3.2. RISK ASSESSMENT PROCESS

Human health risk assessment is a process intended to estimate the risk to a given target organism, system or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system (IPCS, 2004).[41] Human health risk assessment of chemicals refers to methods and techniques that apply to the evaluation of hazards, exposure and harm posed by chemicals, which in some cases may differ from approaches used to assess risks associated with biological and physical agents.[20]

The risk assessment process begins with **problem formulation** and includes four additional steps: 1) **hazard identification**, 2) **hazard characterization**, 3) **exposure**

assessment and 4) **risk characterization** (IPCS, 2004).[41] The risk assessment paradigm, incorporating problem formulation, is summarized in Table 1.[20]

Table 1: Paradigm for risk assessment, including problem formulation

Step	Description	Content
Problem formulation	Establishes the scope and objective of the assessment	Defining the question
		Prior knowledge
		Desired outcomes
Hazard identification	Identifies the type and nature of adverse health effects	Human studies
		Animal-based toxicology studies
		In vitro toxicology studies
		Structure–activity studies
Hazard characterization	Qualitative or quantitative description of inherent properties of an agent having the potential to cause adverse health effects	Selection of critical data set
		Modes/mechanisms of action
		Kinetic variability
		Dynamic variability
		Dose–response for critical effect
Exposure assessment	Evaluation of concentration or amount of a particular agent that reaches a target population	Magnitude
		Frequency
		Duration
		Route
		Extent
Risk characterization	Advice for decision-making	Probability of occurrence
		Severity
		Given population
		Attendant uncertainties

Source: Adapted from IPCS (2009)[42]

Human health risk assessments of chemicals can be performed to evaluate past, current and even future exposures to any chemical found in air, soil, water, food,

consumer products or other materials. They can be quantitative or qualitative in nature. Risk assessments are often limited by a lack of complete information. To be protective of public health, risk assessments are typically performed in a manner that is unlikely to underestimate the actual risk. Regardless, chemical risk assessments rely on scientific understanding of pollutant behaviour, exposure, dose and toxicity. In general terms, **risk depends on the following factors**:

• the **amount of a chemical present** in an environmental medium (e.g. soil, water, air), food and/or a product

• the **amount of contact (exposure) a person** has with the pollutant in the medium

• the **toxicity of the chemical**

Obtaining knowledge to describe these three factors is the cornerstone or foundation of most chemical risk assessments. As these data are not always available, many risk assessments require that estimates or judgements be made regarding some data inputs or characterisations. Consequently, risk assessment results have associated uncertainties, which should be characterised as much as possible.[20]

1.3.3. EFSA – RISK ASSESSMENT OF ACTIVE SUBSTANCES OF PESTICIDES

In the territory of EU the risk management of the active substances of pesticides is addressed by the European Food Safety Authority (EFSA). EFSA's role is to provide independent scientific advice to risk managers based on risk assessments. The European Commission and Member States take risk management decisions on regulatory issues, including approval of active substances and setting of legal limits for pesticide residues in food and feed (maximum residue levels, or MRLs) based on relative proposals made by the EFSA's Pesticide Unit.

Active substances undergo an intensive evaluation process before a decision can be made on approval. EFSA's Pesticides Unit is responsible for the EU peer review of risk assessments of active substances used in plant protection products, in close cooperation with EU Member States. The risk assessment of active substances evaluates whether, when used correctly, these substances are likely to have any direct or indirect harmful effects on human or animal health – for example, through drinking water, food or feed – or on groundwater quality. In addition, the environmental risk assessment aims to evaluate the potential impact on non-target organisms.[2]

Moreover, the Pesticides Unit is responsible for preparing the Annual Report on Pesticide Residues in the EU when also assists the Panel on Plant Protection Products and their Residues (PPR) with administrative and scientific support.

EFSA's Panel on Plant Protection Products and their Residues (PPR) gives scientific advice on issues that cannot be resolved within the peer review of active substances, MRL applications/MRL reviews or when guidance is needed on more generic issues, commonly in the fields of toxicology, ecotoxicology, fate and behaviour and the development of risk assessment practice.[2]

1.3.4. GENERAL PRINCIPLES OF NEUROTOXICITY RISK ASSESSMENT

Neurotoxicity is one of several non-cancer end-points that share common default assumptions and principles. The interpretation of data as indicative of a potential neurotoxic effect involves the evaluation of the validity of the database. There are **four principal questions** that should be addressed:

(1) whether the effects result from exposure

(2) whether the effects are neurotoxicologically significant

(3) whether there is internal consistency between behavioural, physiological, neurochemical and morphological end-points

(4) whether the effects are predictive of what will happen under various conditions.

Addressing these issues can provide a useful framework for evaluating either human or animal studies or the weight of evidence for a chemical (Sette W.F. & MacPhail R.C., 1992; Health Canada, 1994; Hertel R.F., 1996; IPCS, 1999).[17, 51, 52, 53, 54]

1.3.4.1. DEVELOPMENTAL NEUROTOXICITY (DNT) – CHEMICAL HAZARDS IN CHILDREN

In its broadest sense, the environment encompasses all factors that are external to the human host, and children may be exposed to numerous environmental hazards from multiple sources and in a variety of settings. The production and use of toxic

chemicals pose potentially significant environmental threats to the health of children and are the major focus of this document. Global industrialisation, urbanisation, and intensified agriculture, along with increasing patterns of unsustainable consumption and environmental degradation, have released large amounts of toxic substances into the air, water, food and soil.

Although estimates of the burden of disease in children due to environmental chemicals are generally not available, there is clear scientific evidence that exposure to environmental chemicals during different developmental stages can result in a number of adverse outcomes in children and have resulted in an increased incidence of certain childhood diseases. A wide range of chemicals can affect children's health, but a few chemical classes are of particular concern, among them are pesticides. Neonates and infants are also exposed to toxic chemicals (e.g. organochlorine pesticides, heavy metals) through breast milk. The younger child and toddler are susceptible to exposure from chemicals in solid food (e.g. pesticides) and air (e.g. particulate matter) and through dermal exposure (e.g. heavy metals in soil). Exposure to organophosphate pesticides typically occurs in older children and adolescents in rural areas through agricultural work or as bystanders during agricultural pest control.[45]

Exposure to environmental chemicals such as methylmercury, lead, or certain pesticides at levels below those that cause structural defects may produce cellular or molecular changes that are expressed as neurobehavioural (functional) deficits or as increased susceptibility to neurodegenerative diseases much later in life. It has been hypothesised neurotoxic insults during development that result in no observable phenotype at birth or during childhood could manifest later in life as earlier onset of neurodegenerative diseases, such as Parkinson disease. Only a small number of neurotoxins have been adequately studied to address their specific neurobehavioural consequences after prenatal or perinatal exposure.[45]

While adult neurotoxicology evaluates the effects of chemical exposure on relatively stable nervous system structure and function, developmental neurotoxicology addresses the special vulnerabilities of the young. Exposure of pregnant women to alcohol, recreational drugs, therapeutic drugs, nicotine and environmental chemicals may result in the immediate or delayed appearance of neurobehavioural impairment in children. Postnatal exposure of children to chemical agents in the environment, such as lead, also may impair IQ and other indices of neurobehavioural function.

Neurotoxic effects may impair speech and language, attention, general intelligence, "state" regulation and responsiveness to external stimulation, learning and memory, sensory and motor skills, visuospatial processing, affect and temperament, and responsiveness to nonverbal social stimuli. Chemical neurotoxicity may be manifested as decreases in functional capabilities or delays in normative developmental progression.[17]

In humans, the ability of environmental agents to impact various target sites or pathways (e.g. autonomic, peripheral, or central nervous system) as presented above, may arise a diverse range of outcomes that should be considered. To this end, clinical assessment coupled with a battery of standardized assessment tools are likely to be needed. Specifically, gender-specific tools related to behavior should be considered accompanied with standardised clinical assessments available for newborns and paediatric populations; the last should take into account the characteristics or physical/biological properties of the exposure under investigation.[45]

When evaluating toxicological studies in animal models for their relevance to humans, it is also important to keep in mind differences in the timing of critical events in nervous system development between humans and common laboratory animal species. For example, in rodents, considerable brain development occurs during the neonatal period, whereas most of this development occurs during the fetal period in humans.[17]

Regarding animal studies, a draft OECD Test Guideline 426, Developmental Neurotoxicity (DNT) Study, has been developed based on the United States guideline (OECD, 2003).[47] Developmental neurotoxicity studies are designed to develop data on the potential functional and morphological hazards for the nervous system arising in the offspring from exposure of the mother during pregnancy and lactation. The OECD draft test guideline is designed as a separate study, but the observations and measurements can also be incorporated into a two generation study. The neurological evaluation consists of assessment of reflex ontogeny, motor activity, motor and sensory function, and learning and memory; and evaluation of brain weights and neuropathology during postnatal development and adulthood. The behavioural testing includes assessment of the individual animal for a number of relevant behavioural functions, but none of the tests assesses two or more animals together. This means that some behavioural end-points of potential relevance (e.g.

sexual behaviour, play behaviour, social interaction among animals, and aggression) are not assessed using the current test guidelines.[45]

The recent days, the need for alternative testing methods has increased due to the time and cost consuming traditional animal-based testing strategy although the last provides developmental neurotoxicity testing information. Only vary few compounds – including pesticides – have been identified as developmental neurotoxicants (DNToxicants) due to the complexity of the central nervous system and the critical lack of knowledge of neurotoxic mechanisms.[46]

New directives and initiatives for developmental toxicity testing in the United States and Europe will rely increasingly on an integrated and intelligent new testing strategy (Hartung et al., 2013a)[48] utilizing **cell-based in vitro** approaches (Krewski et al., 2010).[49] **Metabolomics** studies represent another major technology for phenotyping biological responses to DNToxicants. **Bioinformatics** plays a key role in mining the information-rich new technologies and making sense of the output by modelling. With interdisciplinary collaboration, toxicology can take advantage of such expert knowledge. The challenge and the opportunity lie in the transition **from MoA models to pathway modelling**. The next challenge will be integrating **multi-omics technologies** for DNT studies on a systems biology level. This kind of integrated approach would lead to a global assessment of adverse effects, indicating the potential of systems biology in terms of pharmacological and toxicological research. Quantitative measurement with multi-omics technologies will bridge the gap between molecular initiating events and relevant adverse outcomes. In addition, this kind of integrated approach will be a significant step towards the better understanding of the mechanisms underlying DNT, which could have profound impact on DNT chemical screening.[46]

2. MATERIALS AND METHODS

2.1. REVIEW OF DATA

Risk assessment is an empirically based process used to estimate the risk that exposure of an individual or population to a chemical, physical or biological agent will be associated with an adverse effect. Risk may be defined as the probability of adverse effects caused under specified conditions by a chemical, physical or biological agent in an organism, a population or an ecological system (OECD/IPCS, 2001).[40] The risk assessment process usually involves four steps: hazard identification, dose-response assessment, exposure assessment and risk characterization (IPCS, 1999).[54]

2.1.1. FOUR STEPS OF RISK ASSESSMENT PROCESS

2.1.1.1. HAZARD IDENTIFICATION

Hazard identification is generally the first step in a risk assessment and is the process used to identify the specific chemical hazard and to determine whether exposure to this chemical has the potential to harm human health. Usually, hazard identification involves establishing the identity of the chemical of interest and determining whether the chemical has been considered hazardous by international organizations and, if so, to what degree.[20]

2.1.1.2. HAZARD CHARACTERISATION

Hazard characterisation typically consists of a qualitative or quantitative description of the inherent properties of the agent having the potential to cause adverse health effects as a result of exposure. There are, however, chemicals that are essential to the human body. Adverse health effects can be observed if exposure to these is below a required level as well as above an upper tolerable level.[20]

Quantitative descriptions often consist of a dose–response assessment, including identification of, for example, a no-observed-adverse-effect level (NOAEL), no-observed-effect level (NOEL) or cancer potency factor, and the application of uncertainty factors to account for interspecies and intra-species variability, data

quality and other uncertainties. This information is used to develop guidance values, such as the TDI and ADI. In turn, human exposure factors, such as intake rates, are then considered to develop guideline values for chemicals in media such as air, water and food.[20]

The guidance values such as the ADI and TDI, which provide an estimate of the amount of chemical that can be taken in orally (mainly by food and drinking-water) by a person without appreciable health risk, are entirely developed from toxicological and epidemiological information. The development of health-based guidance values requires the assessment of the toxicological effect of a chemical in relation to exposure. The relationship between exposure and effect is frequently derived from standardised tests of laboratory animals conducted under controlled conditions. But in some cases, as in arsenic and benzene, these values are based on epidemiological studies (IARC, 1999, 2004).[20, 43, 44]

For effects other than cancer, where a cancer effect in laboratory animals is considered not relevant to humans or where a non-genotoxic mechanism is suggested, health-based guidance values are characterized as thresholds of exposure below which adverse effects are considered unlikely to occur. Benchmarks of risk for non-cancer effects are most frequently expressed as rates of exposure with the units of milligrams per kilogram of body weight per day. Common terms for these values are ADI (e.g. **ADIs have been developed for pesticides by** the Joint FAO/WHO Meeting on Pesticide Residues (**JMPR**) **and for food additives by JECFA**), **TDI**, PTWI, PTMI (developed **for food contaminants** by JECFA) and **acute reference dose (ARfD)** (e.g. developed **for pesticides by JMPR**). These benchmark values are estimates of the amount of a substance in air, food, soil or drinking-water that can be taken in daily, weekly or monthly over a lifetime or other specified period without appreciable health risk.[20]

The ADI and TDI are estimates of exposure rate (sometimes called administered dose) and, as described above, are derived from toxicological and epidemiological information. For this reason, they consider the total (or aggregate) intake of a chemical from all routes and pathways. In contrast, the media-specific guideline values for environmental media take into account conditions specific to the medium of interest and also vary in the extent to which aggregate exposure is considered. For instance, the MRLs are not direct public health limits, but instead reflect agricultural practices and climate scenarios, and they are normally set at levels well below amounts that might lead to an adverse health effect. In contrast, the WHO drinking-

water guidelines are primarily health-based and do attempt to account for exposure through other media.[20]

2.1.1.3. EXPOSURE ASSESSMENT

Exposure assessment is used to determine whether people are in contact with a potentially hazardous chemical and, if so, to how much, by what route, through what media and for how long. Because hazard characterization and risk characterization are dependent upon the route (oral, inhalation, dermal) and duration (short-term, medium-term, long-term) of exposure, knowledge of how and when people may be exposed is relevant to the determination of an appropriate guidance or guideline value. When combined with information on hazard characterization or a guidance or guideline value, exposure information is used to characterize health risks.[20]

The exposure concentration is the concentration of a chemical in a medium with which a person is in contact. These media include air, water, soil, food and consumer products with which people come in contact. Ideally, exposure concentrations will be obtained for media, locations and durations that are representative of potential human contact with a chemical of concern.[20]

The determination of the exposure assessment portion of the risk evaluation is addressed by the following parameters[20]:

• the relevant **routes and pathways** of exposure

• the **environmental media** expected to **contain the chemical**

• the appropriate **duration** of exposure

2.1.1.4. RISK CHARACTERISATION

The last step of a chemical risk assessment – the risk characterisation – is typically a quantitative statement about the estimated exposure relative to the most appropriate health-based guidance value (i.e. ADI, TDI), media-specific quality guideline value or another hazard characterisation value, such as the cancer slope factor. In general, the risk statement is derived by either comparing the estimated exposure with a

guidance or guideline value or calculating the excess lifetime cancer risk associated with the estimated exposure.[20]

Further analysis of this step will follow further below.

2.1.2. EXPOSURE ASSESSMENT

2.1.2.1. ROUTES AND PATHWAYS OF EXPOSURE

One of the major aspects of exposure assessment is determination of routes and pathways of exposure. The **medium of exposure** refers to air, water, soil, food or products (consumer, commercial or industrial) that are thought to contain the chemical of interest. These exposures may occur in occupational or community (i.e. non-occupational) settings or while using products.[20]

Ingestion exposure is associated with chemicals in food, water and soil, both indoors and outdoors. **Inhalation** exposure requires that chemicals be present in air, although it is important to recognise that chemicals with moderate to high vapour pressures and low solubilities can volatilise from water or soil and then be inhaled. Inhalation can also be an important route of exposure to less volatile chemicals, such as polychlorinated biphenyls, when present at elevated concentrations in soil and other solid substrates. Finally, **dermal absorption** requires contact between a chemical and skin, which can occur in water, during contact with soil, in the presence of high concentrations in air and during occupational or consumer use.[20]

The scope of an exposure assessment can be narrowed with information about the chemical and its properties, from which the important exposure media and routes can be inferred. For example, health-relevant exposures to some chemicals, such as ozone, occur through only one medium (in this case air), while for others that can be found in several media, such as lead and pesticides, information about the chemical properties and behaviour can point to environmental media or locations where the highest levels of the chemicals are likely.

In addition, this information can suggest relevant pathways and routes of exposure. **Pathway of exposure** refers to the physical course taken by a chemical as it moves from a source to a point of contact with a person (e.g. through the environment to humans via food). **Route of exposure** refers to intake through ingestion, inhalation or dermal absorption. The exposure routes may have important implications in the hazard characterization step, as the danger posed by a chemical may differ by route.

2.1.2.2. ESTIMATING EXPOSURES: MODELLING OR MEASURING APPROACHES

Generally, risk assessments, especially screening-level risk assessments, are based upon chemical concentrations in environmental media that are relatively easy to access, such as outdoor air, indoor air, lake water, river water and outdoor soil. These concentrations can be determined from a measurement campaign or a modelling effort.[20]

Exposures can be measured directly, estimated using models or generalised from existing data. Each requires that exposures be determined for time periods relevant to possible adverse health outcomes. For example, if the relevant health hazard is chronic in nature, exposure should be long term as well. Measurements, on the other hand, generally provide the most accurate and relevant data, but are the most time and resource intensive, obviating their use for many risk assessments.[20]

2.1.2.2.1. EXPOSURE MODELS

Exposure models generally require information about the concentration of a chemical in a medium and the period of time over which individuals are in contact with the chemical. **Chemical concentrations** can be **measured or** can be **estimated** from **chemical usage** or previous **data**.[20]

Given the complexity of many of these models, it is probable that specialised training on running the models will be necessary. In order to select the appropriate model, information about the geographic and temporal extent of the chemical exposures of interest and the exposed populations of interest should be obtained or otherwise determined.[20]

In case of chemical concentration estimates by models, the information about chemical contact is necessary. This can be obtained using a variety of techniques, including questionnaires or inquiries with affected individuals, demographic data, survey statistics, behaviour observation, activity diaries, activity models or, in the absence of more substantive information, assumptions about behaviour. Using this information, exposures for air, water, food or soil can be estimated using mathematical equations.[20]

2.1.2.2.2. EXPOSURE MEASUREMENTS

Exposure concentrations can also be obtained from measurements, whether they be historical, current or planned for the future. For these concentrations to be truly representative of exposures, they must **measure the concentration** of the **chemical** of interest in environmental **media**, such as air, water and soil, that are **contacted or food** that is **ingested by a person**. Exposure measurements are intended to match the actual media, location and duration that represent the human exposure to the chemical of concern, although this is often not possible to achieve.[20]

Further, some consideration should be given to the **heterogeneity** of exposures within the **relevant population**. For example, if the exposures are similar for all individuals, then measurements made for a relatively small subset of individuals can be generalised to a larger population. Correspondingly, if exposures vary within a population by age, sex or residential location, it is possible that exposure measurements should be made for subsets within each of these groups and generalised to the larger group.[20]

2.1.2.3. DURATION OF EXPOSURE

The duration of exposure is a critical element in assessment and estimation of health risks, as the **relevant period** of exposure is **defined** by **knowledge or theory** of the **mechanisms** of **injury or disease**. Consequently, the duration of exposure is an explicit component of the design of exposure assessments as well as toxicological studies conducted for purposes of hazard identification and hazard characterisation.[20]

Single and short-term exposures over minutes, hours or a day are relevant for chemicals that have an immediate or rapid adverse effect on the body at certain concentrations.[20]

Medium-term or intermediate exposure is important for chemicals that are thought to exert adverse effects over a period of contact that ranges from weeks to months in duration.[20]

For chemicals that pose a hazard as a result of cumulative or long-term low-dose exposure, **long-term average** exposures are most relevant for characterization of adverse effects. Assessments of cancer risk are a special case of long-term exposure for which lifetime average exposure is generally of interest.[20]

2.1.2.4. CONCENTRATION AND RATE OF EXPOSURE

In practice, exposures are generally expressed as either a concentration of the chemical in the exposure medium or a rate of contact with a chemical over a specific duration.[20]

For example, concentrations in contact media are usually expressed in units of micrograms per cubic metre (μg/m^3) for air, micrograms per litre (μg/l) for water and **milligrams per kilogram (mg/kg) for solids such as** soil, dust and **food**. Rate of exposure for a chemical is typically referred to as average daily dose, with units of milligrams of chemical per kilogram of body weight per day (mg/kg body weight per day).[20]

In general, **exposure rate** is **calculated** as the **concentration** of a **chemical** in an exposure **medium** multiplied by the **rate** at which a person **inhales or ingests** that medium, divided by a representative **body weight**.[20]

As shown in Equation 1, the period of exposure and averaging time of exposure are considered explicitly, as well[20]:

$$\text{Exposure rate} = \frac{\text{concentration} \times \text{contact rate} \times \text{exposure duration}}{\text{body weight} \times \text{averaging time}} \quad [1]$$

where:

- concentration is the amount of chemical per mass or volume of the medium
- contact rate is the mass or volume of the medium in contact with the body
- exposure duration is the period of time over which the person is in contact with the chemical
- body weight is the body weight over the averaging time
- averaging time is the period of time over which the exposure is relevant for health risk characterisation

The averaging time used in calculation of average daily dose is typically different for estimation of non-cancer and cancer risks. For chemicals that pose a non-cancer hazard, the average exposure during the period of contact with a chemical is generally the relevant duration of exposure for risk assessment. For cancer risk assessment, however, the averaging time is fixed at a lifetime, which is commonly assumed to be 70 years in risk assessments.[20]

2.1.2.5. BIOMARKERS OF EXPOSURE

Besides the above-described traditional exposure assessment, the use of biological markers is another method with which to evaluate human exposure to a chemical. Biological markers of exposure are **considered measures of internal dose**, whereas exposure describes the contact with a chemical at the boundary between an individual (e.g. skin, mouth or nostrils) and the environment, food or consumer product.

Numerous biological media are available for use in exposure assessment. Selection of sampling media depends on the contaminant of interest, the pattern of exposure, the timing of exposure, the population studied, ease of collection and storage and participant burden.

2.1.3. RISK CHARACTERISATION

Generally, the risk characterization, as a statement, is derived by either comparing the estimated exposure with a guidance or guideline value (i.e. ADI, TDI, ARfD) or calculating the excess lifetime cancer risk associated with the estimated exposure.[20]

- **COMPARISON WITH A GUIDANCE OR GUIDELINE VALUE**

Health-based guidance values or guideline values have been established for a number of chemicals by international organisations. In some cases, the guidance or guideline value is based on an exposure concentration or rate below which adverse effects are considered to be unlikely (threshold chemical). As described in previous section, this approach applies to toxicological effects that occur when a threshold of exposure or dose is exceeded.[20]

Guidance or guideline values are also sometimes established for chemical exposures that are thought to have a continuous hazard characterisation relationship, and there is a theoretical risk of an effect at any level of exposure (non-threshold chemical). Carcinogens and some air pollutants, such as fine particulate matter, are examples of stressors that are considered to pose risk of an adverse health outcome at all levels of exposure. For these substances, guidance or guideline values are exposure concentrations or rates that correspond to levels of risk that have been determined to be tolerable. For instance, long-term average exposure to inorganic arsenic in drinking-water at a certain guideline value (i.e. concentration) may be equivalent to a lifetime cancer risk of 1 in 100 000 (WHO, 2008).[20, 50]

The ADI and TDI are estimates of exposure rate (sometimes called administered dose) and, as described further up, are derived from toxicological and epidemiological information. For this reason, they consider the total (or aggregate) intake of a chemical from all routes and pathways.[20]

For chemicals that have the potential to result in non-cancer effects, risk is frequently characterized as the ratio of the appropriate exposure rate (e.g. the average daily, weekly, monthly intake) to the health-based guidance value: ADI, TDI, PTWI, PTMI or ARfD (often used for pesticide residues and contaminants in food). For exposure to non-cancer chemical hazards in media such as air and drinking-water, the ratio of the chemical concentration in that medium to a reference concentration (e.g. the WHO air quality guideline or the WHO drinking-water quality guideline value) may also be used to assess risk. This ratio is sometimes referred to as the hazard or risk quotient. **A hazard or risk quotient less than 1** indicates that the **chemical exposure is less than the benchmark** and that the exposure is **unlikely** to result in an **adverse effect**. For example, an evaluation of chemical concentrations in exposure media and rates of contact with those media may conclude that the exposure to a chemical is 15 times less than the ADI established by an authoritative organisation as a benchmark for risk of an adverse effect. Conversely, **a hazard or risk quotient greater than 1 indicates** that the **exposure is greater** than the benchmark and that the **sources, pathways and routes of chemical exposure should be evaluated further**.[20]

- **ESTIMATION OF CANCER RISK**

For chemicals that may exert a carcinogenic effect, the risk characterisation is typically expressed as the excess lifetime cancer risk. Characterisation of cancer risk over a lifetime has become a convention primarily because cancer is thought to be a function of long-term rather than short-term exposure. Excess lifetime cancer risk is an estimate of the likelihood of cancer associated with a given level of exposure averaged over a lifetime.[20]

2.1.3.1. CUMULATIVE EXPOSURE RISK ASSESSMENT

Current risk assessment guidelines focus on assessing single chemicals following exposure via single pathways. In order to address aggregrate exposure or cumulative toxicity issues, research is needed to:

(1) test the hypothesis of additivity for chemicals having a similar mode of action;

(2) assess possible non-additive interactions of chemicals with different modes of action; and

(3) study potential interactions of multiple chemicals at doses below those required to produce detectable effects following single exposures.[20]

Humans may be exposed to chemicals at different occasions and in a number of different ways. Exposure to chemicals may occur via the environment (through production and disposal of products), occupational use (during production or product use including consumer ones). Finally, a large number of chemicals are deliberately used for specific applications (pesticides, biocides, veterinary products, food additives), resulting in exposure through food and other routes. All of these may result in exposure of humans through the inhalatory, dermal and oral routes (Delmaar & Van Engelen, 2006).[21, 23]

In the European Union's Technical Guidance Documents (EC, 2003), the term "**aggregate exposure**" is used solely within the scope of consumer exposure assessment and is defined as exposure to the same chemical from multiple sources. "**Combined exposure**" is defined as exposure of the same person to the same substance in the same setting via different routes of entry into the body or from different products containing the same substance. In this abstract, "combined exposure" is considered to be synonymous with "aggregate exposure".[21, 24]

Aggregate risk is the risk associated with multiple pathways /routes of exposure to a single chemical. **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).[21]

Chemicals that act by the same mode of action and/or at the same target cell or tissue often act in a potency-corrected "**Dose Additive**" manner. Where chemicals act independently, by discrete modes of action or at different target cells or tissues, the effects may be additive ("**Effects Additive**" or "**Response Additive**"). Alternatively, chemicals may interact to produce an effect, such that their combined effect "**Departs from Dose Additivity**". Such departures comprise "**Synergy**", where the effect is greater than that predicted on the basis of additivity, and "**Antagonism**", where the effect is less than that predicted on the basis of additivity.[21]

Relevant also to the development of a framework for risk assessment of combined exposures to multiple chemicals is a common understanding of "**Mode of Action**", which has been defined by IPCS, as it figures prominently in approaches to grouping of chemicals for assessment of combined effects. 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. "**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).[21, 22]

As humans are exposed constantly to a wide variety of chemicals, a major challenge in risk assessment is to determine the degree of exposure to multiple chemicals, the hazards associated with such combined exposure and the extent to which chemicals interact. Predicting risk from exposure to chemical mixtures is complex, as chemicals in mixtures can interact in terms of both toxicokinetics and toxicodynamics. Such interactions may result in effects that are either antagonistic or synergistic. The temporal nature of the exposures may play a lead role in determining these interactions.[21]

2.1.3.2. AVAILABLE METHODS FOR COMBINED EXPOSURE RISK ASSESSMENT

There are currently a number of methods used to determine the risk of combined exposure to chemicals. They can be divided into those that simply add the risk from individual chemicals, those that sum effects based on relative potencies and those that rely only on indirect evidence. Most of these have been developed in response to a regulatory need (e.g. toxic equivalency factor [TEF] and dioxins), and each has advantages and disadvantages.[21]

The **Hazard Index** (HI) is the sum of hazard quotients for substances that affect the same target organ or organ system. The hazard quotient is the ratio of the potential exposure to the substance to the level at which no adverse effects are expected (e.g. point of departure, ADI, divided by uncertainty factors). The HI can be used to identify the most risky substances in a mixture, i.e. the chemicals that have the highest health risks based on toxic potential and estimated or measured exposure.[60] A second method, the **Point of Departure Index (PODI)**, is a simple addition method that adds the no-observed-effect levels (or benchmark doses) of individual

chemicals. Neither of these methods includes possible interactions of chemicals that would result in antagonism or synergism.[21]

The **Toxic Equivalent (TEQ)** method was developed for use with compounds that activate the aryl hydrocarbon receptor (Haws et al., 2006; Van den Berg et al., 2006).[55, 56] This is a relative potency method that assumes the additivity of doses of individual components of the mixture after normalisation of the response to a reference chemical. The **Relative Potency Factor (RPF)** method (USEPA, 2000)[57] is a generalised form of the TEQ method and has been used for classes of pesticides and other chemicals. This method also uses dose addition as the default assumption for the effects of mixtures.[21]

Two additional methods have been used when data limitations prevent the use of the above mentioned methods. The **Whole Mixture Approach** (Mumtaz et al., 1993)[58] uses effects data from exposure to the mixture of concern or a sufficiently similar mixture. These data are treated in a risk context similarly to single chemical data. Lastly, the **Threshold of Toxicological Concern (TTC)** has been proposed for use with complex mixtures where no effects data are available (Kroes et al., 2005).[59] This method uses structure–activity relationships to assign exposure thresholds for comparison with the potential exposure level and requires exposure estimates.[21]

Additionally, the **Margin of Exposure (MOE)** of a substance is the NOAEL divided by exposure so that the combined margin of exposure of a mixture (MOE_{mix}) can be calculated accordingly. The margin of exposure index of a mixture is compared to an agreed acceptable threshold. According to EFSA, there are no established criteria for the magnitude of an acceptable MOE_{mix} for mixtures of chemicals but it is widely accepted that at a MOE_{mix} higher than the uncertainty factor of 100 the conclusion can be drawn that the risk of toxicity is unlikely.[60, 61]

Moreover, there are methods for risk assessment of mixtures taking into account interactions. Toxicant interactions may take place during any of the processes that affect the toxic potency of a single compound: adsorption, distribution, metabolism, excretion and activity at the receptor site(s). They may interact chemically, and they may interact by causing different effects at different receptor sites.[62] Interactions can be assumed to occur frequently and often are dose-dependent but, according to EFSA, there is no standard design to evaluate the potential interaction of compounds.[63]

The physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling has been applied to the toxicological interactions of chemical mixtures many years

ago; since then it plays an active role in cumulative risk assessment. Specifically, PBPK/PD modeling can be used to describe the pharmacokinetics, and possibly pharmacodynamics, of a chemical mixture, including possible interaction effects.[60]

For pesticides the suitable substance specific limit value, i.e. the reference level (ref_i) of no concern, usually is the accepted daily intake rate (ADI) relevant to human health but not to certain health endpoints. Calculating the endpoint specific health risk index for a mixture of pesticides by summing up the exposure to limit value ratios requires health endpoint specific limit values assumed to be protective for the selected endpoint. This kind of reference value, e.g. cancer health risk limit values for humans, is usually not available for pesticides. There are two possibilities to deal with this problem: The first is to identify compounds of the mixture affecting the same health endpoint on the basis of available evaluations, to relate exposure to generic ADIs instead of endpoint specific limit values, and then sum up the ratios to derive the index value. The second possibility is to identify compounds of the mixture showing effects when tested with a certain indicator system (e.g. genotoxicity tests), to relate exposure to the substance specific NOAEL derived with this test and sum up these ratios for all components of the mixture.[60]

Grouping of unknown mixtures of unknown substances

Grouping pesticides by effects on indicator systems is of high importance because to date combination toxicology is facing a generic problem: for many potentially toxic substances produced or just present at relevant amounts the mechanism of action is unknown and their toxicity has not been evaluated. With respect to mixtures the approach is based on the identification of relationships between the structure of a substance and its toxicity. In the context of mixtures of chemicals with unknown mode of action the methods might be suitable to sort the compounds of a mixture by predicted modes of action in order to define groups of chemicals for which additive combination toxicology approaches, such as concentration or dose addition, or hazard index related methods, can be applied.[60]

2.2. PRESENT STUDY – METHODS & PARAMETERS

In present study, for the risk assessment of pesticides in food commodities the following methods and data have been used.

The info about the diet (**mean consumption**) was taken by EFSA based on National Diet Survey in Greece related to sub-populations “**lactating women in Greece**” and

"**children in Regional Prefecture of Crete**". The survey comprises **20 food categories** as follows:

- Grains and grain-based products
- Vegetables and vegetable products (including fungi
- Starchy roots and tubers
- Legumes, nuts and oilseeds
- Fruit and fruit products
- Meat and meat products (including edible offal)
- Fish and other seafood (including amphibians, rept
- Milk and dairy products
- Eggs and egg products
- Sugar and confectionary
- Animal and vegetable fats and oils
- Fruit and vegetable juices
- Non-alcoholic beverages (excepting milk based beverages)
- Alcoholic beverages
- Drinking water (water without any additives except
- Herbs, spices and condiments
- Food for infants and small children
- Products for special nutritional use
- Composite food (including frozen products)
- Snacks, desserts, and other foods

The next step was the determination of the dose which was based on various studies. These studies concerned the presence of pesticide residues in all the above food categories mainly in EU and abroad (for international foodstuffs i.e. baby food and those produced abroad i.e. nuts, spices) have been used; totally, **28 studies**.[70-97]

There were identified **197** different **chemical substances** that belong to **42** various **chemical classes** as follows:

Organophosphate, Carbamate, Neonicotinoid, Herbicide, Pyrethroid, Organochlorine, Halogenated, Dispeptide, Oxadiazine, Keto-enol, Azole, Triazine, Strobin, Xylylalanine, Dicarboximide, Organobromide, Pyrimidine, Pyridine, Anilide, Amide, Substituted Benzene, Alkyl Phthalate, OC/Aromatic Ketone, Organophosphate /Carbamate, Morpholine, Amine, Piperidine,

Anthranilic Diamide, Phenylpyrrole, Acylpicolide, Phosphonoglycine, Dithiolane, Urea, Semicarbazone, Diacylhydrazine, Dinitroaniline, Phenol, Phenoxy, Inorganic, Bridged Diphenyl, Quaternary Ammonium Compound, Spinosyn /Macrocyclic Lactone, although some were also **Unclassified**.

The above identification of the each chemical substance classification was taken by the Pesticide Action Network (PAN) Pesticides Database – Chemicals, the Toxicology Network of the U.S. National library of Medicine (TOXNET) and the Inventory of evaluations of pesticides performed by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR).[66, 67, 68] The TOXNET was also the source for the determination of CAS Registry Number for each chemical substance.[67]

The Dose (μg) was expressed as the result of multiplication of the mean consumption (grams per day) taken by the EFSA table as pre-mentioned with the chemical substance residues (μg) identified in each food category. The Total dose was the total sum of all the dose values for each chemical substance in all food categories.

The Daily Intake (μg/g_bw/d) was calculated as the quotient of the total dose divided by the weight of 70kg man (used as standard value for body weight).

The ADI (Acceptable Daily Intake) info was taken both from EFSA and JMPR-Reports. It was given priority to info from EFSA meaning, the established values on EFSA data were used instead those from JMPR for the same chemical. For the rest chemicals that there was no ADI established by EFSA then it was taken by the JMPR data (if set). The EFSA's data is determined as Chemical Hazards data – **OpenFoodTox** [https://dwh.efsa.europa.eu/bi/asp/Main.aspx?rwtrep=400] and released on the EFSA website on 20/01/2017.[69] Regarding JMPR, the ADI info was taken from the WHO website under the name **Inventory of evaluations performed by the Joint Meeting on Pesticide Residues (JMPR)** [http://www.codexalimentarius.org/standards/pesticide-mrls/].[68] Moreover, the same sources (EFSA, JMPR) were used for the toxicological evaluation of all available chemicals under this study.

The RCR equation is used for the determination of the safety of pesticides.

The ADI (Acceptable Daily Intake) was calculated as part of the determination of the **Risk Characterisation Ratio** (**RCR**) for **chronic toxicity risk**. Specifically, this ratio is defined as follows:

Risk characterization ratio (RCR) = Exposure Estimate (Daily Intake) / Acceptable Daily Intake (ADI)

The **Risk Characterisation Ratio** (**RCR**) for the evaluation of **acute toxicity risk** of a chemical substance is defined as follows:

Risk characterisation ratio (RCR) = Exposure Estimate (Daily Intake) / Oral Reference Dose

The Oral Reference Dose values are taken by the **CLARC Master Table** (Annex 1) and its definition is referred at the CLARC website as follows:

Reference dose (RfD) or reference concentration for non-cancer toxicity is an estimate with uncertainty spanning perhaps an order of magnitude of daily exposure to the human population (including sensitive subgroups) that is anticipated to be without appreciable deleterious effects during a lifetime, expressed in units of milligrams per kilogram body weight per day. It is arrived at by dividing empirical data (NOAEL or LOAEL) on effects by uncertainty factors that consider inter- and intraspecies variability, extent of data on all important chronic exposure endpoints, and availability of chronic as opposed to subchronic data. The RfDs are not applicable to non-threshold effects such as cancer. (Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000) Technical Support Document Volume 1: Risk Assessment; WAC 173-340-200).[98]

Since the availability of dose-response data in humans is limited, extrapolation of data from animals to humans usually involves the application of uncertainty factors to the NOAEL/LOAEL or BMD. The NOAEL or BMD/uncertainty factor approach results in a reference dose (RfD) or reference concentration (RfC), which is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The oral RfD and inhalation RfC are applicable to chronic exposure situations and are based on an evaluation of all the noncancer health effects, including neurotoxicity data.[99]

The **Oral Carcinogenic potency factor (CPFo)** is the upper 95th percentile confidence limit of the slope of the dose-response curve and is expressed in unit of measure of $(mg/kg\text{-}day)^{-1}$. (WAC 173-340-200) The cancer potency factor is referred to by EPA as a slope factor.[98]

The **Margin of Safety (MoS)** is the opposite of **Risk Characterisation Ratio (RCR)**. It is used to describe the safety of a chemical substance; it is expressed as

Margin of Safety (MoS) = Oral Reference Dose / Exposure Estimate (Daily Intake)

Another parameter to be taken into account is the **Cancer Risk** which is calculated as follows:

Cancer Risk = Daily Intake x Oral Cancer Potency Factor (CPFo)

whereas, “Oral Cancer Potency Factor” is expressed in kg-day/mg.

Moreover, the **JMPR monographs** have been used as a source for the toxicological evaluation of the chemical substances upon any kind of neurotoxicity end-point. The JMPR is an international expert scientific group that is administered jointly by FAO and WHO in 2010. JMPR, which consists of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group on Pesticide Residues, has been meeting regularly since 1963. During the meetings, the WHO Core Assessment Group is responsible for reviewing toxicological and related data and for estimating, where possible, the ADIs as well as the ARfDs of the pesticides under consideration

Finally, the **cumulative risk** factor has been calculated in order to determine the potential outcome to human health resulting **from chronic exposure** to various pesticides through daily food consumption. Moreover, the **cumulative cancer risk** from exposure to pesticides through diet has been evaluated.

The cumulative risk for chronic exposure is the outcome of the following equation:

Cumulative Risk = 1-(1-A)*(1-B)*(1-C)*…*(1-Z)

whereas, A, B, C…Z refers to the **RCR for chronic risk** defined for each chemical substance.

Likewise, the cumulative cancer risk is the outcome of the following equation:

Cumulative Risk = 1-(1-A)*(1-B)*(1-C)*…*(1-Z)

whereas, A, B, C…Z refers to the **cancer risk value** defined for each chemical substance.

3. RESULTS – DISCUSSION

This dissertation aims in evaluating the safety level of the presence of pesticide residues in food through daily food consumption in Greece. As mentioned before, the exposure information is used to characterise health risks. Since there are many toxicological effects correlated with pesticides, this study is focused mainly on neurotoxicity end-point. Moreover, an approach of the potential cumulative risk is also accomplished.

Therefore, the following parameters were calculated before proceeding with the main results.

The determination of dose (μg) is based on the multiplication of the mean consumption value (g/day) of a food category by the residue value (μg/g) of the active substance detected in the same food category. By adding all the values under each chemical substance the total dose (μg) for the specific chemical is calculated. The total dose is used in order to define the "**daily intake (μg/g_bw/d)**" which refers to the exposure concentration.

The daily intake is the quotient of the total dose divided by the weight of 70kg (7000g) man (used as standard value for body weight).

According to the current dissertation, one hundred ninety seven (197) different pesticides identified and quantified in various twenty (20) food categories totally.

3.1. LACTATING WOMEN

The results for the sub-population "**lactating women in Greece**" are as follows:

The sixty six (66) out of 197 chemicals can present acute risk according to the results.

The **Risk Characterisation Ratio** (**RCR**) for the evaluation of **acute risk** of a chemical substance is defined as follows:

Risk characterisation ratio (RCR) = Exposure Estimate (Daily Intake) / Oral Reference Dose

When the quotient is <1 the risk to the human health due to the chemical is considered small; specifically, the smaller than the one, the less minimum the risk.

Referring to the data, the results revealed that the majority of the active substances are much less than the one. Sixty six (66) out of 197 substances, or the 33.5% of them, are bearing greater health risk at different level. Among the 33.5%, the 7.6% or five (5) chemical substances were presenting the higher acute risk as higher than one, while about the 13.6% and 28.8%, or 9 and 19 substances accordingly, were following with a risk less closer to one (10^{-1} and 10^{-2} respectively).

The most risky chemicals – higher than one – were **dimethoate (OPP), methamidophos (OPP), parathion-methyl (OPP), propoxur (CARB), triadimefon (AZO).** The four of them belong to the chemical class of organophosphates (OPP), whilst the other two to carbamates (CARB) and azoles chemical group (AZO).

Those following most risky chemicals (10^{-1}) were aldrin (OC), carbofuran (CARB), chlorpyrifos (OPP), dichlorvos (OPP/CARB), ethion (OPP), lindane (OC), heptachlor epoxide (OC), imazalil (AZO) and trifluralin (DINITROANILINE). Otherwise, in percentage, the 33.3% belongs to OC, 22.22% to OPP, 11.11% to CARB, 11.11% to OPP/CARB, 11.11% to AZO and 11.11% to DINITROANILINE.

The **Risk Characterisation Ratio** (**RCR**) for the evaluation of **chronic risk** of a chemical substance is defined as follows:

Risk characterization ratio (RCR) = Exposure Estimate (Daily Intake) / Acceptable Daily Intake (ADI)

The ADI is expressed in mg/kg-bw/day as the daily intake that equals to μg/g-bw/day; the necessary conversions have been performed.

According to the results, there were some chemicals equal to zero but all less than one. From 154 chemical substances, there were six (6) chemical substances equal zero (0) and eleven (11) much closer (10^{-1}) to the one but not above it which can be regarded as the most risky ones to human health among the rest ones. Those with zero value were **demeton-S-methyl sulfoxide (OPP), ethoprofos (OPP), maneb group (CARB), methamidophos (OPP), propoxur (CARB) and triadimephon (AZO)**, although those with 10^{-1} value were pirimiphos – methyl (OPP), oxamyl (CARB), omethoate (OPP), imazalil (AZO), etofenprox (PYR), dimethoate (OPP), diazinon (OPP), chlorpyrifos (OPP), chlorfenvinphos (OPP), carbofuran (CARB) and carbaryl (CARB). All of them comprise the 11% which summarise the 3.9% for zero value with the 7.1% for 10^{-1} value, as those followed with 10^{-2} comprise the 31.2%.

Specifically, the 48 less risky chemical substances accompanied with 10^{-2} belong to the chemical classes of dinitroaniline (1), organophosphates (11), organochlorines (5), azoles (7), phenoxy (1), carbamates (7), dicarboximide (3), pyrethrines (4), organophosphate/carbamate (1), anilides (1), amides (1), pyrimidines /pyridines (2), strobines (1), urea (1), spinosyn macrocyclic lactone (1) and morpholine (1).

The **cumulative risk** for chronic exposure equals with 1.0E+00 which in other terms means that is marginal safe and potential concerns towards health safety cannot be avoided and/or ignored.

The opposite of **Risk Characterisation Ratio (RCR)** is the **Margin of Safety (MoS)** that is used to describe the safety of a chemical substance; it is expressed as

Margin of Safety (MoS) = Oral Reference Dose / Exposure Estimate (Daily Intake)

The larger than the one the quotient the safer the chemical is. The results show that the less safe ones and those much closer to the one were those with 10^0, 10^1 and 10^2 values which if expressed in percentage comprise 14.5%, 30.6% and 30.6% accordingly. Moreover, there was one value expressed as 10^{-1} that stands for **parathion-methyl (OPP)** which can be regarded as the most risky of all particular substances. Those attached with 10^0 are Aldrin (OC), carbofuran (CARB), chlorpyrifos (OPP), dichlorvos (OPP/CARB), ethion (OPP), lindane (OC), heptachlor epoxide (OC), imazalil (AZO) and trifluralin (DINITROANILINE).

Referring to the chemical classes, in the particular case, the majority of the less safe chemicals belong to the chemical groups of organophosphates and organochlorines, followed by carbamates, azoles and dinitroaniline.

The **Cancer Risk** is calculated as follows:

Cancer Risk = Daily Intake x Oral Cancer Potency Factor (CPFo)

whereas, Oral Cancer Potency Factor is expressed in kg-day/mg.

The smaller the product of multiplication the safer the chemical is regarding the cancer risk.

The calculation of the **cumulative risk for cancer** reveals that there is such risk and equals with 3.1E-04.

The calculations for the cancer risk show that aldrin (OC), BHC – benzene hexachloride (OC), dichlorvos (OPP/CARB), lindane (OC), heptachlor (OC), heptachlor epoxide (OC) and trifluralin (DINITROANILINE), which belong to chemical classes of organochlorines, dinitroanilines and organophosphates/carbamates, are considered having the higher risk among those identified. It seems that the chemical class of organochlorines is having the highest cancer risk comparing with the other chemical classes.

3.2. CHILDREN IN REGIONAL PREFECTURE OF CRETE

The results for the sub-population "**children in Regional Prefecture of Crete**" are as follows:

The fifty six (56) out of 197 chemicals can present acute neurotoxicity effects according to the toxicity tests performed.

The **Risk Characterisation Ratio** (**RCR**) for the evaluation of **acute risk** of a chemical substance is defined as follows:

Risk characterisation ratio (RCR) = Exposure Estimate (Daily Intake) / Oral Reference Dose

When the quotient is <1 the risk to the human health due to the chemical is considered small; specifically, the smaller than the one, the less minimum the risk.

Referring to the data, the results revealed that the majority of the active substances are much less than the one. Sixty (60) out of 197 substances, or the 30% of them, are bearing greater health risk at different level. Among the 30%, the 10% or six (6) chemical substances were presenting the higher acute risk as closer to one (10^{-1}), while about the 23% and 38%, or 14 and 23 substances accordingly, were following with a risk less closer to one (10^{-2} and 10^{-3} respectively).

The most risky chemicals (10^{-1}) were **chlorpyrifos, dimethoate, ethion, parathion-methyl, heptachlor epoxide and imazalil**. The first three belong to the chemical class of organophosphates (OPP), the fourth to the organochlorines (OC) and the last to the azoles chemical group (AZO).

Those following most risky chemicals (10^{-2}) were aldrin (OC), carbofuran (CARB), chlorpyrifos-methyl (OPP), cypermethrin (PYR), 4,4'-DDT (OC), diazinon (OPP), dichlorvos (OPP/CARB), lindane or γ-HCH (ORGANOCHLORINE), iprodione

(DICARBOXIMIDE), linuron (UREA), malathion (OPP), phosmet (OPP), pirimiphos-methyl (OPP) and trifluthrin (DINITROANILINE).

Those with chemical risk accompanied with 10^{-3} were acephate, bifenthrin, carbaryl, chlorpropham, chlorothalonil, cyromazine, DDT, dieldrin, endosulfan, endrin, fluvalinate, glyphosate, heptachlor, metalaxyl, methomyl, myclobutanil, oxamyl, prochloraz, propargite, propiconazole, quinalphos, thiophanate-methyl, vinclozolin.

The **Risk Characterisation Ratio** (**RCR**) for the evaluation of **chronic risk** of a chemical substance is defined as follows:

Risk characterization ratio (RCR) = Exposure Estimate (Daily Intake) / Acceptable Daily Intake (ADI)

The ADI is expressed in mg/kg-bw/day as the daily intake that equals to μg/g-bw/day.

According to the results, there were no chemicals above the one. From 138 chemical substances, only seven (7) chemical substances were much closer (10^{-1}) to the one but not above it, these can be regarded as the most risky ones to human health among the rest ones. These were **omethoate (OPP), imazalil (AZO), heptachlor epoxide (OC), dimethoate (OPP), chlorpyrifos (OPP), chlorfenvinphos (OPP), carbofuran (CARB)**. All of them comprise the 5.07% as those followed with 10^{-2} comprise the 23.19% and those with 10^{-3} comprise the 28.98%.

Specifically, the 32 less riskier chemical substances accompanied with 10^{-2} belong to the chemical classes of dinitroaniline (1), organophosphates (9), organochlorides (2), azoles (6), phenoxy (1), carbamates (6), dicarboximide (1), pyrethrines (4), organophosphate/carbamate (1) and morpholine (1).

The **cumulative risk** for chronic exposure equals with 9.1E-01 which although is less than the one it still is very close to it arising potential concerns towards health safety.

The opposite of **Risk Characterisation Ratio (RCR)** is the **Margin of Safety (MoS)** that is used to describe the safety of a chemical substance; it is expressed as

Margin of Safety (MoS) = Oral Reference Dose / Exposure Estimate (Daily Intake)

The larger than the one the quotient the safer the chemical is. The results show that the less safest ones and those much closer to the one where those with 10^{0}, 10^{1} and

10^2 values which if expressed in percentage comprise 10%, 21.67% and 40% accordingly. Those attached with 10^0 are chlorpyrifos (OPP), dimethoate (OPP), ethion (OPP), heptachlor epoxide (OC), imazalil (AZO), parathion-methyl (OPP). As before, under this parameter, the majority of the less safe chemicals belong to the chemical group of organophosphates and the other two to azoles and organochlorines.

The **Cancer Risk** is calculated as follows:

Cancer Risk = Daily Intake x Oral Cancer Potency Factor (CPFo)

whereas, Oral Cancer Potency Factor is expressed in kg-day/mg.

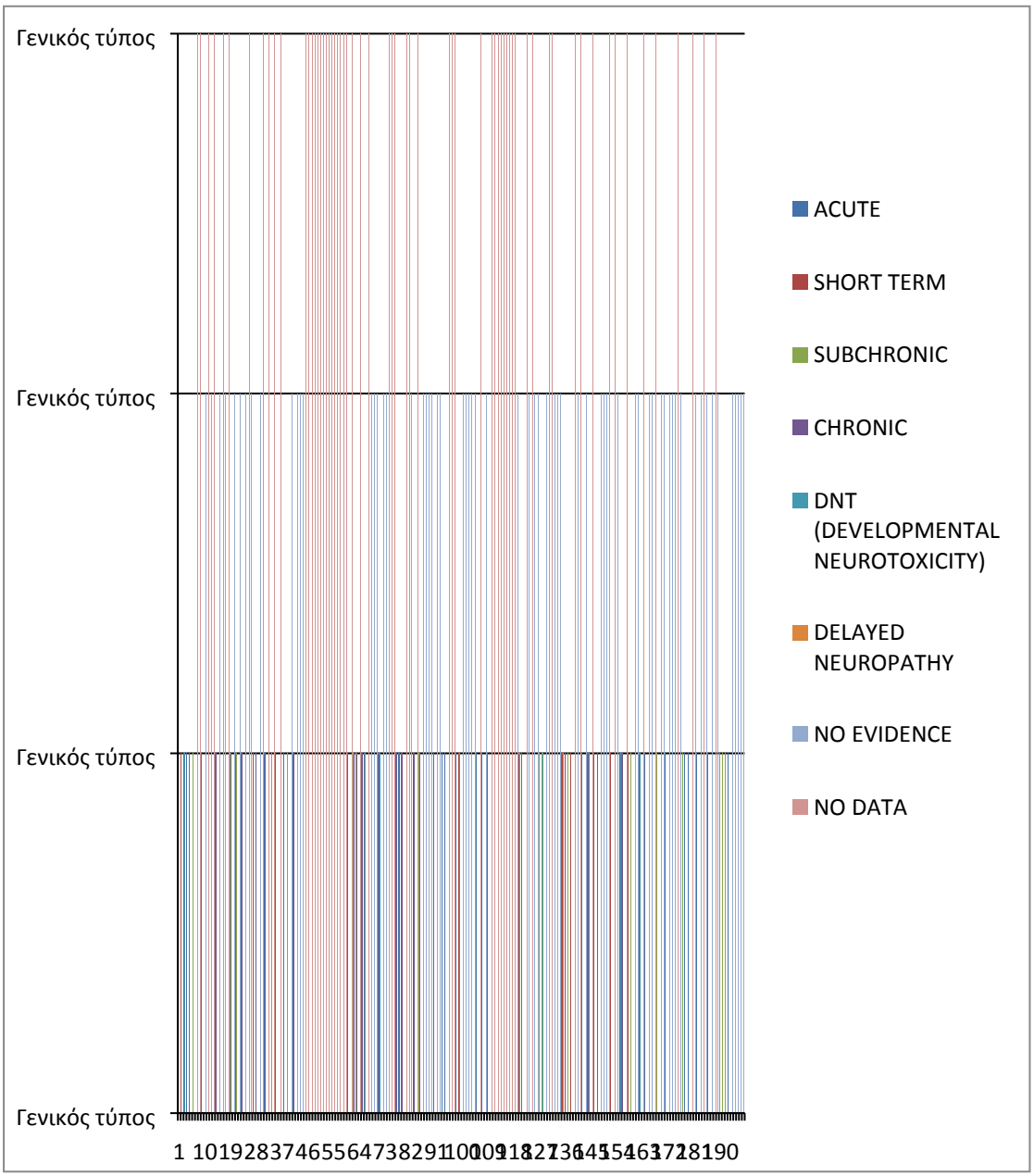
The smaller the product of multiplication the safer the chemical is regarding the cancer risk.

The calculation of the **cumulative risk for cancer** reveals that there is such risk and equals with 2.1E-04.

The calculations for the cancer risk show that Aldrin (OC), dichlorvos (OPP/CARB), lindane (OC) and heptachlor epoxide (OC), which belong to chemical class of organochlorines (OC) and organophosphates /carbamates (OPP/CARB), are considered having the higher risk among those identified. It seems that the chemical class of organochlorines is having the highest cancer risk comparing with other chemical classes.

3.3. NEUROTOXICITY EVALUATION

Referring to the toxicological evaluation of the chemical substances, this was performed either by EFSA and /or JMPR as pre-mentioned. The results of the evaluation on each identified pesticide revealed six (6) **kind of neurotoxicity** as end-points such as, **acute, short term, sub-chronic, chronic, developmental (DNT) and delayed neuropathy**, and are being presented on the following graph – Table 2:



4. CONCLUSION

The role of Pesticides or Plant Protection Products (PPRs) is preventing crops from being damaged or destroyed by disease and pests and thus, maintaining crop yields. As the majority of pesticides are chemicals, by their nature, are potentially toxic to other organisms, including humans. Therefore, since their presence in food and feed is considered unavoidable nowadays, they need to be used safely and disposed of properly.

The presence of pesticide residues in foodstuffs has been associated with human health effects many times through research and clinical observations. One of the major points was their toxicological effects of which neurotoxicity has being investigated in this study. Additionally, cancer risk is the other principal point that is taken into account through this study. Moreover, an approach of the potential cumulative risk due to chronic exposure and cancer risk is also accomplished.

The result of the **Risk Characterisation Ratio** (**RCR**) for the evaluation of **acute or chronic risk** of a chemical substance is assessed as follows:

When the quotient is <1 the risk to the human health due to the chemical is considered small; specifically, the smaller than the one, the less minimum the risk.

Regarding the sub – population "**lactating women"**, the **acute risk** assessment revealed that the majority of active substances are much less than the one. Among 197 substances, the 7.6% or five (5) chemical substances were presenting acute risk with values as higher than one. These were **dimethoate (OPP)**, **methamidophos (OPP)**, **parathion-methyl (OPP)**, **propoxur (CARB)**, **triadimefon (AZO)**. The four of them belong to the chemical class of organophosphates (OPP), whilst the other two to carbamates (CARB) and azoles chemical group (AZO).

The acute risk for the above pesticides can be regarded as high for the sub – population "**lactating women in Greece**".

Regarding the sub – population "**children in regional prefecture of Crete**", the **acute risk** assessment revealed that the majority of the active substances are much less than the one. Among 197 substances, the 10% or six (6) chemical substances

were presenting the higher acute risk as closer to one. These were **chlorpyrifos, dimethoate, ethion, parathion-methyl, heptachlor epoxide and imazalil**. The first four belong to the chemical class of organophosphates (OPP), whilst the fifth to the organochlorines (OC) and the last to the azoles chemical group (AZO).

The acute risk for the above pesticides can be considered as low for the sub – population "**children in regional prefecture of Crete**".

Comparing the results for acute risk of the two sub – populations, it seems that the difference can be regarded to the diversity of daily intakes due to variant mean consumption of each food category between lactating women and children. Moreover, they share two chemical substances that belong to the chemical class of organophosphates (OPP). This chemical class can be assumed as having the highest acute risk for both sub – populations examined.

According to the **chronic risk** assessment results for the sub – population "**lactating women"**, there were some chemicals equal to zero but all less than one. From 154 chemical substances, the 3.9% of them or six (6) chemical substances equal zero (0) which were **demeton-S-methyl sulfoxide (OPP), ethoprofos (OPP), maneb group (CARB), methamidophos (OPP), propoxur (CARB) and triadimephon (AZO)**.

With regard to the **chronic risk** assessment results for the sub – population "**children in regional prefecture of Crete**", there were no chemicals above the one. Among 138 chemical substances, only the 5.07% or seven (7) chemical substances were much closer to the one but none above it, which were **omethoate (OPP), imazalil (AZO), heptachlor epoxide (OC), dimethoate (OPP), chlorpyrifos (OPP), chlorfenvinphos (OPP), carbofuran (CARB)**.

Comparing the results for chronic risk of the two sub – populations, it seems that they are in line with no one value exceeding the one. Concerning of the individual impact of the identified chemical substances, it seems that they do not pose any significant chronic risk to human health through food consumption.

In other terms, the chronic risk for the detected pesticides can be regarded as low for both sub–populations "**lactating women in Greece**" and "**children in regional prefecture of Crete**".

As in the acute risk assessment, the majority of the chemical substances for both sub – populations having the higher impact in the chronic risk assessment belong to the

chemical class of organophosphates (OPP), followed by carbamates and azoles chemical classes.

Concerning of the **cumulative risk** for **chronic exposure** for "**lactating women**", it equals with 1.0E+00 which in other terms means that is marginal safe and potential concerns towards health safety cannot be avoided and/or ignored. In the case of "**children in regional prefecture of Crete**", the **cumulative risk** for **chronic exposure** equals with 9.1E-01 which although is less than the one it is still very close thus, arising potential concerns towards human health safety.

Regarding the **cumulative risk assessment for cancer** for "**lactating women**", it reveals that there is such risk and equals with 3.1E-04.

According to the results, the pesticides considering having the highest impact risk on cumulative cancer are **aldrin (OC), BHC – benzene hexachloride (OC), dichlorvos (OPP/CARB), lindane (OC), heptachlor (OC), heptachlor epoxide (OC)** and **trifluralin (DINITROANILINE)**, which belong to the chemical classes of organochlorines, dinitroanilines and organophosphates/carbamates. Obviously, the chemical class of organochlorines is having the highest cumulative cancer risk comparing with the other chemical classes.

Likewise, the **cumulative risk assessment for cancer** for "**children in the prefecture of Crete**" reveals that there is such risk and equals with 2.1E-04.

Moreover, the pesticides identified bearing the highest impact on cumulative cancer risk are: **aldrin (OC), dichlorvos (OPP/CARB), lindane (OC) and heptachlor epoxide (OC)**, which belong to chemical class of organochlorines (OC) and organophosphates /carbamates (OPP/CARB). It seems that the chemical class of organochlorines is having the highest cumulative cancer risk comparing with other chemical classes.

Comparing the results for cumulative cancer risk, it is revealed that there is such risk in both sub – populations examined. Additionally, both populations almost share the same pesticides identified with the highest impact of cumulative cancer risk on human health through diet, bringing also the chemical class of organochlorines at the top of such impact risk in this study.

Referring to the toxicological evaluation of the chemical substances upon neurotoxicity that was performed either by EFSA and /or JMPR, the results are as follows:

A/A	KIND OF NEUROTOXICITY	NUMBER OF CHEMICALS
1	ACUTE	57
2	SHORT TERM	16
3	SUB-CHRONIC	26
4	CHRONIC	23
5	DNT (DEVELOPMENTAL NEUROTOXICITY)	7
6	DELAYED NEUROPATHY	2
7	NO EVIDENCE (OF NEUROTOXICITY)	65
8	NO DATA (OF NEUROTOXICITY AND /OR ANY TOXICITY)	64

The majority of the pesticides identified (197) in this study may induce acute neurotoxicity (57), followed by sub-chronic (26) and chronic neurotoxicity (23). Sixteen out of 197 pesticides can induce short term neurotoxicity, whilst seven and two may develop developmental neurotoxicity (DNT) and delayed neuropathy respectively.

Additionally, the toxicological evaluation of sixty five (65) pesticides revealed that they do not induce any kind of neurotoxicity while sixty four (64) out of 197 were missing toxicological data.

In conclusion, the exposure of sensitive population, such as lactating women and children, to pesticide residues in foodstuffs may provoke acute and chronic toxicity effects and cancer risk to their health.

According to the latest scientific development internationally that gave rise to cumulative risk assessment, cumulative effects will only occur when chemicals with similar toxicological properties present on food are consumed together. Thus, the development of pesticides with better qualitative and quantitative attributes with regard to elimination of severe toxicity effects to human health should be progressed and also combined with effective pest management training to all stakeholders.

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LIST OF ACRONYMS AND ABBREVIATIONS

AChE	acetylcholinesterase
ADI	acceptable daily intake
ARfD	acute reference dose
ATSDR	Agency for Toxic Substances and Disease Registry (USA)
BMD	benchmark dose
CAC	Codex Alimentarius – International Food Standards
CAS	Chemical Abstracts Service
CNS	central nervous system
CPFo	oral cancer (or carcinogenic) potency factor
DNT	Developmental Neurotoxicity
EC	European Commission
EEC	European Economic Community
EFSA	European Food Safety Agency
EHC	Environmental Health Criteria
EPA	Environmental Protection Agency
ERPs	event – related potentials
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
GAP	good agricultural practice
HI	hazard index
IARC	International Agency for Research on Cancer
IQ	Intelligence Quotient
IPCS	International Programme on Chemical Safety
IPM	Integrated pest management
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues

MoA	mode of action
MOE	margin of exposure
MOEmix	margin of exposure of a mixture
MoS	margin of safety
MRI	magnetic resonance imaging
MRL	maximum residue limit
NINDS	National Institute of Neurological Disorders
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OECD	Organisation for Economic Co-operation and Development
P300	component of the auditory event-related brain potential
PAN	Pesticide Action Network
PBPK/PD	physiologically based pharmacokinetic/pharmacodynamics
PET	positron emission tomography
PNS	peripheral nervous system
PODI	point of departure index
PPR	Panel on Plant Protection Products and their Residues (EFSA)
PPPs	plant protection products
PRIMo	Pesticide Residue Intake Model
PTMI	provisional tolerable monthly intake
PTWI	provisional tolerable weekly intake
qEEG	quantitative electroencephalography
RIVM	National Institute for Public Health and the Environment (Netherlands)
RMS	Rapporteur Member State
RCR	risk characterisation ratio
RfC	reference concentration
RfD	reference dose
RPF	Relative Potency Factor

RIVM	National Institute for Public Health and the Environment (Netherlands)
SARs	Structure-activity relationships
SEPs	somatosensory evoked potentials
SF	slope factor
SPECT	single photon emission computerized tomography
TDI	tolerable daily intake
TEF	toxic equivalency factor
TEQ	toxic equivalent
TOCP	tri-*o*-cresylphosphate
TOXNET	toxicology data network
TTC	threshold of toxicological concern
UN	United Nations
UNEP	United Nations Environment Programme
USA/US	United States of America
USEPA	United States Environmental Protection Agency
WAC	Washington Administrative Code
WHO	World Health Organization

ANNEX 1

Chemical Name	CAS #	RfDo Oral Reference Dose (mg/kg-day)	CPFo Oral Cancer Potency Factor (kg-day/mg)
acenaphthene	83-32-9	6,00E-02	
acenaphthylene	208-96-8		
acephate	30560-19-1	4,00E-03	8,70E-03
acetaldehyde	75-07-0		
acetochlor	34256-82-1	2,00E-02	
acetone	67-64-1	9,00E-01	
acetone cyanohydrin	75-86-5		
acetonitrile	75-05-8		
acetophenone	98-86-2	1,00E-01	
acifluorfen, sodium	62476-59-9	1,30E-02	
acrolein	107-02-8	5,00E-04	
acrylamide	79-06-1	2,00E-03	5,00E-01
acrylic acid	79-10-7	5,00E-01	
acrylonitrile	107-13-1	4,00E-02	5,40E-01
alachlor	15972-60-8	1,00E-02	5,60E-02
alar	1596-84-5	1,50E-01	1,80E-02
aldicarb	116-06-3	1,00E-03	
aldicarb sulfone	1646-88-4	1,00E-03	
aldrin	309-00-2	3,00E-05	1,70E+01

ally	74223-64-6	2,50E-01	
allyl alcohol	107-18-6	5,00E-03	
allyl chloride	107-05-1		2,10E-02
aluminum	7429-90-5	1,00E+00	
aluminum phosphide	20859-73-8	4,00E-04	
amdro	67485-29-4	3,00E-04	
ametryn	834-12-8	9,00E-03	
aminophenol;m-	591-27-5	8,00E-02	
aminopyridine;4-	504-24-5		
amitraz	33089-61-1	2,50E-03	
ammonia	7664-41-7		
ammonium perchlorate	7790-98-9	7,00E-04	
ammonium sulfamate	7773-06-0	2,00E-01	
aniline	62-53-3	7,00E-03	5,70E-03
anthracene	120-12-7	3,00E-01	
antimony	7440-36-0	4,00E-04	
antimony pentoxide	1314-60-9	5,00E-04	
antimony potassium tartrate	28300-74-5	9,00E-04	
antimony tetroxide	1332-81-6	4,00E-04	
antimony trioxide	1309-64-4		
apollo	74115-24-5	1,30E-02	
aramite	140-57-8	5,00E-02	2,50E-02
aroclor 1016	12674-11-2	7,00E-05	7,00E-02
aroclor 1254	11097-69-1	2,00E-05	2,00E+00
aroclor 1260	11096-82-5		2,00E+00
arsenic, inorganic	7440-38-2	3,00E-04	1,50E+00
arsine	7784-42-1	3,50E-06	

assure	76578-14-8	9,00E-03	
asulam	3337-71-1	5,00E-02	
atrazine	1912-24-9	3,50E-02	2,30E-01
avermectin B1	65195-55-3	4,00E-04	
azobenzene	103-33-3		1,10E-01
barium and compounds	7440-39-3	2,00E-01	
barium cyanide	542-62-1		
baygon	114-26-1	4,00E-03	
bayleton	43121-43-3	3,00E-02	
baythroid	68359-37-5	2,50E-02	
benefin	1861-40-1	3,00E-01	
benomyl	17804-35-2	5,00E-02	
bentazon	25057-89-0	3,00E-02	
benzaldehyde	100-52-7	1,00E-01	
benzene	71-43-2	4,00E-03	5,50E-02
benzenethiol	108-98-5	1,00E-03	
benzidine	92-87-5	3,00E-03	2,30E+02
benzo(g,h,i)perylene	191-24-2		
benzo[a]anthracene	56-55-3		7,30E-01
benzo[a]pyrene	50-32-8		7,30E+00
benzo[b]fluoranthene	205-99-2		7,30E-01
benzo[k]fluoranthene	207-08-9		7,30E-02
benzoic acid	65-85-0	4,00E+00	
benzotrichloride	98-07-7		1,30E+01
benzyl alcohol	100-51-6	1,00E-01	
benzyl chloride	100-44-7	2,00E-03	1,70E-01
beryllium	7440-41-7	2,00E-03	

beta-chloronaphthalene	91-58-7	8,00E-02	
bidrin	141-66-2	1,00E-04	
biphenthrin	82657-04-3	1,50E-02	
biphenyl;1,1-	92-52-4	5,00E-01	8,00E-03
bis(2-chloro-1-methyl-ethyl)ether	108-60-1	4,00E-02	7,00E-02
bis(2-chloroethyl)ether	111-44-4		1,10E+00
bis(2-chloroisopropyl) ether	39638-32-9		
bis(2-ethylhexyl) phthalate	117-81-7	2,00E-02	1,40E-02
bis(chloromethyl)ether	542-88-1		2,20E+02
bisphenol a	80-05-7	5,00E-02	
boron	7440-42-8	2,00E-01	
bromate	15541-45-4	4,00E-03	7,00E-01
bromodichloromethane	75-27-4	2,00E-02	6,20E-02
bromoethene	593-60-2		
bromoform	75-25-2	2,00E-02	7,90E-03
bromomethane	74-83-9	1,40E-03	
bromophos	2104-96-3	5,00E-03	
bromoxynil	1689-84-5	2,00E-02	
bromoxynil octanoate	1689-99-2	2,00E-02	
butadiene;1,3-	106-99-0		3,40E+00
butanol;n-	71-36-3	1,00E-01	
butyl benzyl phthalate	85-68-7	2,00E-01	1,90E-03
butylate	2008-41-5	5,00E-02	
butylphthalyl butylglycolate	85-70-1	1,00E+00	
butyric acid;4-(2-methyl-4-chlorophenoxy)-	94-81-5	1,00E-02	
cacodylic acid	75-60-5	2,00E-02	
cadmium (soil and nonpotable surface water)	7440-43-9a	1,00E-03	

cadmium (potable groundwater and surface water)	7440-43-9	5,00E-04	
calcium cyanide	592-01-8	1,00E-03	
caprolactam	105-60-2	5,00E-01	
captafol	2425-06-1	2,00E-03	1,50E-01
captan	133-06-2	1,30E-01	2,30E-03
carbaryl	63-25-2	1,00E-01	
carbazole	86-74-8		
carbofuran	1563-66-2	5,00E-03	
carbon disulfide	75-15-0	1,00E-01	
carbon tetrachloride	56-23-5	4,00E-03	7,00E-02
carbophenothion	786-19-6		
carbosulfan	55285-14-8	1,00E-02	
carboxin	5234-68-4	1,00E-01	
chloral	75-87-6		
chloral hydrate	302-17-0	1,00E-01	
chloramben	133-90-4	1,50E-02	
chloranil	118-75-2		4,00E-01
chlordane	57-74-9	5,00E-04	3,50E-01
chloride	16887-00-6		
chlorimuron-ethyl	90982-32-4	2,00E-02	
chlorine	7782-50-5	1,00E-01	
chlorine cyanide	506-77-4	5,00E-02	
chlorine dioxide	10049-04-4	3,00E-02	
chlorite	7758-19-2	3,00E-02	
chloro-1,1-difluoroethane;1-	75-68-3		
chloro-1,3-butadiene;2-	126-99-8	2,00E-02	

chloro-2-methylaniline hydrochloride;4-	3165-93-3		4,60E-01
chloro-2-methylaniline;4-	95-69-2	3,00E-03	1,00E-01
chloroacetic acid	79-11-8	2,00E-03	
chloroacetophenone;2-	532-27-4		
chloroaniline;p-	106-47-8	4,00E-03	2,00E-01
chlorobenzene	108-90-7	2,00E-02	
chlorobenzilate	510-15-6	2,00E-02	1,10E-01
chlorobenzoic acid;p-	74-11-3	3,00E-02	
chlorobenzotrifluoride;4-	98-56-6	3,00E-03	
chlorobutane;1-	109-69-3	4,00E-02	
chlorodifluoromethane	75-45-6		
chloroform	67-66-3	1,00E-02	3,10E-02
chloromethane	74-87-3		
chloromethyl methyl ether	107-30-2		2,40E+00
chloronitrobenzene;o-	88-73-3	3,00E-03	3,00E-01
chloronitrobenzene;p-	100-00-5	1,00E-03	6,30E-03
chlorophenol;2-	95-57-8	5,00E-03	
chlorophenyl methyl sulfide;p-	123-09-1		
chlorophenyl methyl sulfone;p-	98-57-7		
chlorophenyl methyl sulfoxide;p-	934-73-6		
chloropropane;2-	75-29-6		
chlorothalonil	1897-45-6	1,50E-02	3,10E-03
chlorotoluene;o-	95-49-8	2,00E-02	
chlorpropham	101-21-3	2,00E-01	
chlorpyrifos	2921-88-2	1,00E-03	
chlorpyrifos-methyl	5598-13-0	1,00E-02	
chlorsulfuron	64902-72-3	5,00E-02	

chlorthiophos	21923-23-9	8,00E-04	
chromium (total)	7440-47-3		
chromium(III)	16065-83-1	1,50E+00	
chromium(VI)	18540-29-9	3,00E-03	
chrysene	218-01-9		7,30E-03
coke oven emissions	8007-45-2		
coal tar creosote	8001-58-9		
copper	7440-50-8	4,00E-02	
copper cyanide	544-92-3	5,00E-03	
cresol;m-	108-39-4	5,00E-02	
cresol;o-	95-48-7	5,00E-02	
cresol;p-	106-44-5	1,00E-01	
crotonaldehyde	123-73-9	1,00E-03	1,90E+00
cumene	98-82-8	1,00E-01	
cyanazine	21725-46-2	2,00E-03	8,40E-01
cyanide	57-12-5	6,00E-04	
cyanogen	460-19-5	1,00E-03	
cyanogen bromide	506-68-3	9,00E-02	
cyclohexane	110-82-7		
cyclohexanone	108-94-1	5,00E+00	
cyclohexylamine	108-91-8	2,00E-01	
cyclopentadiene	542-92-7		
cyhalothrin/karate	68085-85-8	5,00E-03	
cypermethrin	52315-07-8	1,00E-02	
cyromazine	66215-27-8	7,50E-03	
dacthal	1861-32-1	1,00E-02	
dalapon, sodium salt	75-99-0	3,00E-02	

danitol	39515-41-8	2,50E-02	
db;2,4-	94-82-6	8,00E-03	
ddd	72-54-8		2,40E-01
dde	72-55-9		3,40E-01
ddt	50-29-3	5,00E-04	3,40E-01
decabromodiphenyl ether	1163-19-5	7,00E-03	7,00E-04
demeton	8065-48-3	4,00E-05	
di(2-ethylhexyl)adipate	103-23-1	6,00E-01	1,20E-03
diallate	2303-16-4		6,10E-02
diazinon	333-41-5	7,00E-04	
dibenzo[a,h]anthracene	53-70-3		7,30E+00
dibenzofuran	132-64-9	1,00E-03	
dibromo-3-chloropropane;1,2-	96-12-8	2,00E-04	8,00E-01
dibromobenzene;1,4-	106-37-6	1,00E-02	
dibromochloromethane	124-48-1	2,00E-02	8,40E-02
di-butyl phthalate	84-74-2	1,00E-01	
dicamba	1918-00-9	3,00E-02	
dichloro-2-butene;1,4-	764-41-0		
dichlorobenzene;1,2-	95-50-1	9,00E-02	
dichlorobenzene;1,3-	541-73-1		
dichlorobenzene;1,4-	106-46-7	7,00E-02	5,40E-03
dichlorobenzidine;3,3'-	91-94-1		4,50E-01
dichlorodifluoromethane	75-71-8	2,00E-01	
dichloroethane;1,1-	75-34-3	2,00E-01	5,70E-03
dichloroethane;1,2-	107-06-2	6,00E-03	9,10E-02
dichloroethylene,1,2- (mixed isomers)	540-59-0	9,00E-03	
dichloroethylene;1,1-	75-35-4	5,00E-02	

dichloroethylene;1,2-,cis	156-59-2	2,00E-03	
dichloroethylene;1,2-,trans	156-60-5	2,00E-02	
dichlorophenol;2,4-	120-83-2	3,00E-03	
dichlorophenoxyacetic acid;2,4-	94-75-7	1,00E-02	
dichloropropane;1,2-	78-87-5	9,00E-02	3,60E-02
dichloropropanol;2,3-	616-23-9	3,00E-03	
dichloropropene;1,3-	542-75-6	3,00E-02	1,00E-01
dichlorvos	62-73-7	5,00E-04	2,90E-01
dicofol	115-32-2		
dicyclopentadiene	77-73-6	8,00E-03	
dieldrin	60-57-1	5,00E-05	1,60E+01
diethyl phthalate	84-66-2	8,00E-01	
diethylene glycol	111-46-6		
diethylene glycol dinitrate	693-21-0		
diethylene glycol monobutyl ether	112-34-5	3,00E-02	
diethylene glycol monoethyl ether	111-90-0	6,00E-02	
diethylformamide	617-84-5	1,00E-03	
diethyl-p-nitrophenylphosphate	311-45-5		
diethylstilbesterol	56-53-1		3,50E+02
difenzoquat	43222-48-6	8,00E-02	
diflubenzuron	35367-38-5	2,00E-02	
difluoroethane;1,1-	75-37-6		
diisopropyl methylphosphonate	1445-75-6	8,00E-02	
dimethipin	55290-64-7	2,00E-02	
dimethoate	60-51-5	2,00E-04	
dimethoxybenzidine;3,3'-	119-90-4		1,60E+00
dimethyl phthalate	131-11-3		

dimethyl terephthalate	120-61-6	1,00E-01	
dimethylamine	124-40-3		
dimethylaniline hydrochloride;2,4-	21436-96-4		5,80E-01
dimethylaniline;2,4-	95-68-1	2,00E-03	2,00E-01
dimethylaniline;N,N-	121-69-7	2,00E-03	
dimethylbenzidine;3,3'-	119-93-7		1,10E+01
dimethylformamide;N,N-	68-12-2	1,00E-01	
dimethylhydrazine;1,1-	57-14-7	1,00E-04	
dimethylhydrazine;1,2-	540-73-8		5,50E+02
dimethylphenol;2,4-	105-67-9	2,00E-02	
dimethylphenol;2,6-	576-26-1	6,00E-04	
dimethylphenol;3,4-	95-65-8	1,00E-03	
dinitrobenzene;m-	99-65-0	1,00E-04	
dinitrobenzene;o-	528-29-0	1,00E-04	
dinitrobenzene;p-	100-25-4	1,00E-04	
dinitro-o-cyclohexyl phenol;4,6-	131-89-5	2,00E-03	
dinitrophenol;2,4-	51-28-5	2,00E-03	
dinitrotoluene mixture; 2,4-/2,6-	25321-14-6	9,00E-04	4,50E-01
dinitrotoluene;2,4-	121-14-2	2,00E-03	3,10E-01
dinitrotoluene;2,6-	606-20-2	3,00E-04	1,50E+00
di-n-octyl phthalate	117-84-0	1,00E-02	
dinoseb	88-85-7	1,00E-03	
dioxane;1,4-	123-91-1	3,00E-02	1,00E-01
diphenamid	957-51-7	3,00E-02	
diphenylamine	122-39-4	2,50E-02	
diphenylhydrazine;1,2-	122-66-7		8,00E-01
diquat	85-00-7	2,20E-03	

direct black 38	1937-37-7		7,40E+00
direct blue 6	2602-46-2		7,40E+00
direct brown 95	16071-86-6		6,70E+00
direct sky blue	2610-05-1		
disulfoton	298-04-4	4,00E-05	
dithiane;1,4-	505-29-3	1,00E-02	
diuron	330-54-1	2,00E-03	
dodine	2439-10-3	4,00E-03	
endosulfan	115-29-7	6,00E-03	
endothall	145-73-3	2,00E-02	
endrin	72-20-8	3,00E-04	
epichlorohydrin	106-89-8	6,00E-03	9,90E-03
epoxybutane	106-88-7		
ethephon	16672-87-0	5,00E-03	
ethion	563-12-2	5,00E-04	
ethoxyethanol acetate;2-	111-15-9	1,00E-01	
ethoxyethanol;2-	110-80-5	9,00E-02	
ethyl acetate	141-78-6	9,00E-01	
ethyl acrylate	140-88-5		4,80E-02
ethyl chloride	75-00-3		
ethyl dipropylthiocarbamate;S-	759-94-4	2,50E-02	
ethyl ether	60-29-7	2,00E-01	
ethyl methacrylate	97-63-2	9,00E-02	
ethyl p-nitrophenyl phenylphosphorothioate	2104-64-5	1,00E-05	
ethylbenzene	100-41-4	1,00E-01	
ethylene cyanohydrin	109-78-4	7,00E-02	
ethylene diamine	107-15-3	9,00E-02	

ethylene dibromide (EDB)	106-93-4	9,00E-03	2,00E+00
ethylene glycol	107-21-1	2,00E+00	
ethylene glycol monobutyl ether (EGBE)	111-76-2	1,00E-01	
ethylene oxide	75-21-8		3,10E-01
ethylene thiourea	96-45-7	8,00E-05	4,50E-02
ethylphthalyl ethylglycolate	84-72-0	3,00E+00	
express	101200-48-0	8,00E-03	
fenamiphos	22224-92-6	2,50E-04	
fensulfothion	115-90-2		
fluometuron	2164-17-2	1,30E-02	
fluoranthene	206-44-0	4,00E-02	
fluorene	86-73-7	4,00E-02	
fluoride	16984-48-8	4,00E-02	
fluorine, soluble fluoride	7782-41-4	6,00E-02	
fluridone	59756-60-4	8,00E-02	
flurprimidol	56425-91-3	2,00E-02	
flutolanil	66332-96-5	6,00E-02	
fluvalinate	69409-94-5	1,00E-02	
folpet	133-07-3	1,00E-01	3,50E-03
fomesafen	72178-02-0		1,90E-01
fonfos	944-22-9	2,00E-03	
formaldehyde	50-00-0	2,00E-01	
formic acid	64-18-6	9,00E-01	
fosetyl-al	39148-24-8	3,00E+00	
furan	110-00-9	1,00E-03	
furazolidone	67-45-8		3,80E+00
furfural	98-01-1	3,00E-03	

furium	531-82-8		1,50E+00
furmecyclox	60568-05-0		3,00E-02
glufosinate-ammonium	77182-82-2	4,00E-04	
glycidaldehyde	765-34-4	4,00E-04	
glyphosate	1071-83-6	1,00E-01	
gross alpha particle activity	unavailable20		
gross beta particle activity	unavailable21		
haloxyfop-methyl	69806-40-2	5,00E-05	
harmony	79277-27-3	1,30E-02	
heptachlor	76-44-8	5,00E-04	4,50E+00
heptachlor epoxide	1024-57-3	1,30E-05	9,10E+00
heptane;n-	142-82-5		
hexabromobenzene	87-82-1	2,00E-03	
hexabromodiphenyl ether; 2,2',4,4',5,5'-	68631-49-2	2,00E-04	
hexachlorobenzene	118-74-1	8,00E-04	1,60E+00
hexachlorobutadiene	87-68-3	1,00E-03	7,80E-02
hexachlorocyclohexane;alpha	319-84-6	8,00E-03	6,30E+00
hexachlorocyclohexane;beta-	319-85-7		1,80E+00
hexachlorocyclohexane;delta-	319-86-8		
hexachlorocyclohexane;technical	608-73-1		1,80E+00
hexachlorocyclopentadiene	77-47-4	6,00E-03	
hexachlorodibenzo-p-dioxin, mixture	19408-74-3		6,20E+03
hexachloroethane	67-72-1	7,00E-04	4,00E-02
hexachlorophene	70-30-4	3,00E-04	
hexamethylene diisocyanate;1,6-	822-06-0		
hexane;n-	110-54-3	6,00E-02	
hexazinone	51235-04-2	3,30E-02	

hydrazine	302-01-2		3,00E+00
hydrazine sulfate	10034-93-2		3,00E+00
hydrogen chloride	7647-01-0		
hydrogen cyanide	74-90-8	6,00E-04	
hydrogen sulfide	7783-06-4		
hydroquinone	123-31-9	4,00E-02	6,00E-02
imazalil	35554-44-0	1,30E-02	
imazaquin	81335-37-7	2,50E-01	
indeno[1,2,3-cd]pyrene	193-39-5		7,30E-01
iprodione	36734-19-7	4,00E-02	
iron	7439-89-6	7,00E-01	
isobutyl alcohol	78-83-1	3,00E-01	
isophorone	78-59-1	2,00E-01	9,50E-04
isopropalin	33820-53-0	1,50E-02	
isopropyl methyl phosphonic acid	1832-54-8	1,00E-01	
isoxaben (not in HSDB)	82558-50-7	5,00E-02	
lactofen	77501-63-4	2,00E-03	
lead	7439-92-1		
lead alkyls	unavailable02		
lindane	58-89-9	3,00E-04	1,10E+00
linuron	330-55-2	2,00E-03	
lithium perchlorate	7791-03-9	7,00E-04	
londax	83055-99-6	2,00E-01	
malathion	121-75-5	2,00E-02	
maleic anhydride	108-31-6	1,00E-01	
maleic hydrazide	123-33-1	5,00E-01	
malononitrile	109-77-3	1,00E-04	

mancozeb	8018-01-7	3,00E-02	
maneb	12427-38-2	5,00E-03	
manganese	7439-96-5	1,40E-01	
mephosfolan	950-10-7	9,00E-05	
mepiquat chloride	24307-26-4	3,00E-02	
mercuric chloride	7487-94-7	3,00E-04	
mercury	7439-97-6		
merphos	150-50-5	3,00E-05	
metalaxyl	57837-19-1	6,00E-02	
methacrylonitrile	126-98-7	1,00E-04	
methamidosphos	10265-92-6	5,00E-05	
methanol	67-56-1	2,00E+00	
methidathion	950-37-8	1,00E-03	
methomyl	16752-77-5	2,50E-02	
methoxy-5-nitroaniline;2-	99-59-2		4,90E-02
methoxychlor	72-43-5	5,00E-03	
methoxyethanol acetate;2-	110-49-6	8,00E-03	
methoxyethanol;2-	109-86-4	5,00E-03	
methyl acetate	79-20-9	1,00E+00	
methyl acrylate	96-33-3	3,00E-02	
methyl ethyl ketone	78-93-3	6,00E-01	
methyl isobutyl ketone	108-10-1	8,00E-02	
methyl mercury	22967-92-6	1,00E-04	
methyl methacrylate	80-62-6	1,40E+00	
methyl naphthalene;1-	90-12-0	7,00E-02	2,90E-02
methyl naphthalene;2-	91-57-6	4,00E-03	
methyl parathion	298-00-0	2,50E-04	

methyl styrene	25013-15-4	6,00E-03	
methyl styrene, alpha	98-83-9	7,00E-02	
methyl tert-butyl ether	1634-04-4		1,80E-03
methyl-4-chlorophenoxy-acetic acid;2-	94-74-6	5,00E-04	
methyl-5-nitroaniline;2-	99-55-8	2,00E-02	9,00E-03
methylaniline hydrochloride;2-	636-21-5		1,30E-01
methylaniline;2-	95-53-4		
methylcyclohexane	108-87-2		
methylene bis(2-chloroaniline);4,4'-	101-14-4	2,00E-03	1,00E-01
methylene bis(n,n'-dimethyl)aniline;4,4'-	101-61-1		4,60E-02
methylene bromide	74-95-3	1,00E-02	
methylene chloride	75-09-2	6,00E-03	2,00E-03
methylene diphenyl diisocyanate (MDI)	101-68-8		
methylene diphenyl diisocyanate (PMDI)	9016-87-9		
methylenebisbenzenamine;4,4-	101-77-9		1,60E+00
methylhydrazine	60-34-4	1,00E-03	
metolachlor	51218-45-2	1,50E-01	
metribuzin	21087-64-9	2,50E-02	
mevinphos	7786-34-7		
mirex	2385-85-5	2,00E-04	1,80E+01
molinate	2212-67-1	2,00E-03	
molybdenum	7439-98-7	5,00E-03	
monochloramine	10599-90-3	1,00E-01	
monochlorobutanes (not in HSDB)	unavailable03		
naled	300-76-5	2,00E-03	
naphthalene	91-20-3	2,00E-02	
napropamide	15299-99-7	1,00E-01	

n-butylbenzene	104-51-8	5,00E-02	
niagara blue 4B	2429-74-5		
nickel refinery dust	unavailable04	1,10E-02	
nickel soluble salts	7440-02-0	2,00E-02	
nickel subsulfide	12035-72-2	1,10E-02	1,70E+00
nitrate	14797-55-8	1,60E+00	
nitric oxide	10102-43-9		
nitrite	14797-65-0	1,00E-01	
nitroaniline, 2-	88-74-4	1,00E-02	
nitrobenzene	98-95-3	2,00E-03	
nitrofurantoin	67-20-9	7,00E-02	
nitrofurazone	59-87-0		1,30E+00
nitrogen dioxide	10102-44-0		
nitroguanidine	556-88-7	1,00E-01	
nitropropane;2-	79-46-9		
nitrosodiethanolamine;N-	1116-54-7		2,80E+00
nitrosodiethylamine;N-	55-18-5		1,50E+02
nitrosodimethylamine;N-	62-75-9	8,00E-06	5,10E+01
nitroso-di-n-butylamine;N-	924-16-3		5,40E+00
nitroso-di-n-propylamine;N-	621-64-7		7,00E+00
nitrosodiphenylamine;N-	86-30-6		4,90E-03
nitrosomethylvinylamine,n-	4549-40-0		
nitroso-n-ethylurea;n-	759-73-9		2,70E+01
nitroso-N-methylethylamine;N-	10595-95-6		2,20E+01
nitroso-n-methylurea,n-	684-93-5		1,20E+02
nitrosopyrrolidine;N-	930-55-2		2,10E+00
nitrotoluene, m-	99-08-1	1,00E-04	

nitrotoluene, o-	88-72-2	9,00E-04	2,20E-01
nitrotoluene, p-	99-99-0	4,00E-03	1,60E-02
nitrotoluenes;o-,m-,p-	1321-12-6		
norflurazon	27314-13-2	4,00E-02	
nustar	85509-19-9	7,00E-04	
octabromodiphenyl ether	32536-52-0	3,00E-03	
octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine	2691-41-0	5,00E-02	
octamethylpyrophosphoramide	152-16-9	2,00E-03	
oryzalin	19044-88-3	5,00E-02	
oxadiazon	19666-30-9	5,00E-03	
oxamyl	23135-22-0	2,50E-02	
oxyfluorfen	42874-03-3	3,00E-03	
paclobutrazol	76738-62-0	1,30E-02	
pah	unavailable05		
paraquat	4685-14-7		
parathion	56-38-2	6,00E-03	
pebulate	1114-71-2	5,00E-02	
pendimethalin	40487-42-1	4,00E-02	
pentabromo-6-chloro-cyclohexane;1,2,3,4,5-	87-84-3		2,30E-02
pentabromodiphenyl ether; 2,2',4,4',5-	60348-60-9	1,00E-04	
pentabromodiphenyl ethers	32534-81-9	2,00E-03	
pentachlorobenzene	608-93-5	8,00E-04	
pentachloronitrobenzene	82-68-8	3,00E-03	2,60E-01
pentachlorophenol	87-86-5	5,00E-03	4,00E-01
perchlorate and perchlorate salts	7601-90-3	7,00E-04	
permethrin	52645-53-1	5,00E-02	

perthane	72-56-0		
pH	unavailable19		
phenanthrene	85-01-8		
phenmedipham	13684-63-4	2,50E-01	
phenol	108-95-2	3,00E-01	
phenylenediamine, p-	106-50-3	1,90E-01	
phenylenediamine;m-	108-45-2	6,00E-03	
phenylenediamine;o-	95-54-5		4,70E-02
phenylmercuric acetate	62-38-4	8,00E-05	
phenylphenol;2-	90-43-7		1,90E-03
phorate	298-02-2	2,00E-04	
phosmet	732-11-6	2,00E-02	
phosphine	7803-51-2	3,00E-04	
phosphoric acid	7664-38-2	4,90E+01	
phosphorus	7723-14-0	2,00E-05	
phthalic acid;p-	100-21-0	1,00E+00	
phthalic anhydride	85-44-9	2,00E+00	
picloram	1918-02-1	7,00E-02	
pirimiphos-methyl	29232-93-7	1,00E-02	
polybrominated biphenyls	67774-32-7	7,00E-06	3,00E+01
polychlorinated biphenyls (PCBs)	1336-36-3		2,00E+00
potassium cyanide	151-50-8	2,00E-03	
potassium perchlorate	7778-74-7	7,00E-04	
potassium silver cyanide	506-61-6	5,00E-03	
prochloraz (not in HSDB)	67747-09-5	9,00E-03	1,50E-01
profluralin	26399-36-0	6,00E-03	
prometon	1610-18-0	1,50E-02	

prometryn	7287-19-6	4,00E-03	
pronamide	23950-58-5	7,50E-02	
propachlor	1918-16-7	1,30E-02	
propanil	709-98-8	5,00E-03	
propargite	2312-35-8	2,00E-02	
propargyl alcohol	107-19-7	2,00E-03	
propazine	139-40-2	2,00E-02	
propham	122-42-9	2,00E-02	
propiconazole	60207-90-1	1,30E-02	
propionic acid;(2-methyl-4-chlorophenoxy)2-	93-65-2	1,00E-03	
propylbenzene;n-	103-65-1	1,00E-01	
propylene glycol	57-55-6	2,00E+01	
propylene glycol dinitrate;1,2-	6423-43-4		
propylene glycol monoethyl ether	52125-53-8	7,00E-01	
propylene glycol monomethyl ether	107-98-2	7,00E-01	
propylene oxide	75-56-9		2,40E-01
pursuit	81335-77-5	2,50E-01	
pydrin	51630-58-1	2,50E-02	
pyrene	129-00-0	3,00E-02	
pyridine	110-86-1	1,00E-03	
quinalphos	13593-03-8	5,00E-04	
quinoline	91-22-5		3,00E+00
radium 226	unavailable24		
radium 226 and 228	unavailable23		
rdx	121-82-4	3,00E-03	1,10E-01
refractory ceramic fibers	unavailable07		
resmethrin	10453-86-8	3,00E-02	

ronnel	299-84-3	5,00E-02	
rotenone	83-79-4	4,00E-03	
s,s;s-tributylphosphorotrithioate	78-48-8	3,00E-05	
savey	78587-05-0	2,50E-02	
sec-butylbenzene	135-98-8	1,00E-01	
selenious acid	7783-00-8	5,00E-03	
selenium and compounds	7782-49-2	5,00E-03	
selenourea	630-10-4		
sethoxydim	74051-80-2	9,00E-02	
silver	7440-22-4	5,00E-03	
silver cyanide	506-64-9	1,00E-01	
simazine	122-34-9	5,00E-03	1,20E-01
sodium azide	26628-22-8	4,00E-03	
sodium cyanide	143-33-9	1,00E-03	
sodium diethyldithiocarbamate	148-18-5	3,00E-02	2,70E-01
sodium fluoroacetate	62-74-8	2,00E-05	
sodium metavanadate	13718-26-8	1,00E-03	
sodium perchlorate	7601-89-0	7,00E-04	
strontium	7440-24-6	6,00E-01	
strychnine	57-24-9	3,00E-04	
styrene	100-42-5	2,00E-01	
sulfate	unavailable17		
systhane	88671-89-0	2,50E-02	
tcdd;2,3,7,8- (Low organic) (dioxin)	1746-01-6	7,00E-10	1,30E+05
tebuthiuron	34014-18-1	7,00E-02	
temephos	3383-96-8	2,00E-02	

terbacil	5902-51-2	1,30E-02	
terbufos	13071-79-9	2,50E-05	
terbutryn	886-50-0	1,00E-03	
tert-butylbenzene	98-06-6	1,00E-01	
tetrabromodiphenyl ether 2,2',4,4'	5436-43-1	1,00E-04	
tetrachlorobenzene;1,2,4,5-	95-94-3	3,00E-04	
tetrachloroethane;1,1,1,2-	630-20-6	3,00E-02	2,60E-02
tetrachloroethane;1,1,2,2-	79-34-5	2,00E-02	2,00E-01
tetrachloroethylene (PCE)	127-18-4	6,00E-03	2,10E-03
tetrachlorophenol;2,3,4,6-	58-90-2	3,00E-02	
tetrachlorotoluene;p,a,a,a,-	5216-25-1		2,00E+01
tetrachlorvinphos	961-11-5	3,00E-02	2,40E-02
tetraethyl dithiopyrophosphate	3689-24-5	5,00E-04	
tetraethyl lead	78-00-2	1,00E-07	
tetrafluoroethane;1,1,1,2-	811-97-2		
thallic oxide	1314-32-5		
thallium acetate	563-68-8	6,00E-06	
thallium carbonate	6533-73-9	2,00E-05	
thallium chloride	7791-12-0	6,00E-06	
thallium nitrate	10102-45-1	7,00E-06	
thallium selenite	12039-52-0		
thallium(I) sulfate	7446-18-6	2,00E-05	
thallium, soluble salts	7440-28-0	1,00E-05	
thiobencarb	28249-77-6	1,00E-02	
thiocyanomethylthiobenzothiazole;2-	21564-17-0	3,00E-02	
thiofanox	39196-18-4	3,00E-04	
thiophanate-methyl	23564-05-8	8,00E-02	

thiram	137-26-8	5,00E-03	
tin	7440-31-5	6,00E-01	
tnt	118-96-7	5,00E-04	3,00E-02
toluene	108-88-3	8,00E-02	
toluene diisocyanate mixture;2,4-/2,6-	26471-62-5		
toluenediamine;2,4-	95-80-7		
toluenediamine;2,5-	95-70-5	2,00E-04	1,80E-01
toluenediamine;2,6-	823-40-5		
toluidine;p-	106-49-0	4,00E-03	3,00E-02
total dissolved solids	unavailable18		
toxaphene	8001-35-2		1,10E+00
tp;2,4,5-	93-72-1	8,00E-03	
tph, diesel range organics	unavailable09		
tph, heavy oils	unavailable10		
tph, mineral oil	unavailable11		
tph: gasoline range organics, benzene present*	unavailable25		
tph: gasoline range organics, no detectable benzene*	unavailable08		
tralomethrin	66841-25-6	7,50E-03	
triallate	2303-17-5	1,30E-02	
triasulfuron	82097-50-5	1,00E-02	
tribromobenzene;1,2,4-	615-54-3	5,00E-03	
tributyltin oxide	56-35-9	3,00E-04	
trichloro-1,2,2-trifluoroethane;1,1,2-	76-13-1	3,00E+01	
trichloroaniline hydrochloride;2,4,6-	33663-50-2		2,90E-02
trichloroaniline;2,4,6-	634-93-5	3,00E-05	7,00E-03

trichlorobenzene;1,2,4-	120-82-1	1,00E-02	2,90E-02
trichloroethane;1,1,1-	71-55-6	2,00E+00	
trichloroethane;1,1,2-	79-00-5	4,00E-03	5,70E-02
trichloroethylene (TCE)	79-01-6	5,00E-04	Guidance
trichlorofluoromethane	75-69-4	3,00E-01	
trichlorophenol;2,4,5-	95-95-4	1,00E-01	
trichlorophenol;2,4,6-	88-06-2	1,00E-03	1,10E-02
trichlorophenoxyacetic acid;2,4,5-	93-76-5	1,00E-02	
trichloropropane;1,1,2-	598-77-6	5,00E-03	
trichloropropane;1,2,3-	96-18-4	4,00E-03	3,00E+01
trichloropropene;1,2,3-	96-19-5	3,00E-03	
tridiphane	58138-08-2	3,00E-03	
triethylamine	121-44-8		
trifluralin	1582-09-8	7,50E-03	7,70E-03
trihalomethanes, total (TTHMs)	unavailable13		
trimethyl phosphate	512-56-1	1,00E-02	2,00E-02
trimethylbenzene;1,2,4-	95-63-6		
trimethylbenzene;1,3,5-	108-67-8	1,00E-02	
trinitrobenzene;1,3,5-	99-35-4	3,00E-02	
trinitrophenylmethylnitramine	479-45-8	2,00E-03	
uranium, soluble salts	unavailable12	3,00E-03	
vanadium	7440-62-2	5,00E-03	
vanadium pentoxide	1314-62-1	9,00E-03	
vanadyl sulfate	27774-13-6		
vernam	1929-77-7	1,00E-03	
vinclozolin	50471-44-8	2,50E-02	
vinyl acetate	108-05-4	1,00E+00	

vinyl chloride	75-01-4	3,00E-03	Guidance
warfarin	81-81-2	3,00E-04	
white mineral oil	8012-95-1	3,00E+00	
xylene;m-	108-38-3	2,00E-01	
xylene;o-	95-47-6	2,00E-01	
xylene;p-	106-42-3	2,00E-01	
xylenes	1330-20-7	2,00E-01	
zinc	7440-66-6	3,00E-01	
zinc cyanide	557-21-1	5,00E-02	
zinc phosphide	1314-84-7	3,00E-04	
zineb	12122-67-7	5,00E-02	

ANNEX 2

TOXICOLOGICAL MONOGRAPHS – JMPR

PESTICIDE RISK ASSESSMENT OF ACTIVE SUBSTANCE – EFSA

These monographs, published by the World Health Organization, contain detailed descriptions of the biological and toxicological data used in JMPR's evaluations, as well as conclusions such as intake assessments for the pesticides under consideration. In addition, they provide full references to the relevant literature. The information and endpoints contained in the evaluations are also summarized in the reports published as FAO Plant Production and Protection Papers.

1. ACEPHATE

Source: ACEPHATE 3–16 JMPR 2005

Kind of Neurotoxicity: acute/short-term neurotoxicity

The Meeting established an ADI of 0–0.03 mg/kg bw based on the NOAEL of 0.25 mg/kg bw per day from the study of repeated doses in humans and an overall safety factor of 10. The Meeting established an ARfD of 0.1 mg/kg bw on the basis of the NOAEL of 1.2 mg/kg bw from the study of single doses in humans and an overall safety factor of 10.

The overall safety factor of 10 was derived by dividing the default value of 10 by 2 (because inhibition of acetylcholinesterase activity depends on the Cmax) and by multiplying by 2 (because some uncertainty remains with respect to the in-vivo sensitivity to inhibition of human brain acetylcholinesterase activity relative to that of erythrocyte acetylcholinesterase activity, since brain acetylcholinesterase may be more sensitive than erythrocyte acetylcholinesterase).

Neurotoxicity/delayed neurotoxicity

NOAEL for acute neurotoxicity	1.2 mg/kg bw (humans)
NOAEL in short-term study of neurotoxicity	0.25 mg/kg bw per day (humans)
No signs of delayed polyneuropathy (hens)	

Summary	Value	Study	Safety factor

ADI	0–0.03 mg/kg bw	Human, 28-day study	10
ARfD	0.1 mg/kg bw	Human, single-dose study	10

2. ACETAMIPRID

Source: ACETAMIPRID 3–92 JMPR 2011

Kind of Neurotoxicity: Acute /Developmental neurotoxicity

Acetamiprid did not cause delayed neuropathy in hens.

Neurotoxicity/delayed neurotoxicity

Acute neurotoxicity target/critical effect	Motor activity and increased frequency of urination
Lowest relevant acute neurotoxic	NOAEL 10 mg/kg bw
Subchronic neurotoxicity target/critical effect	Not neurotoxic (rats)
Developmental neurotoxicity target/critical effect	Deficits in auditory startle response
Lowest relevant developmental neurotoxic NOAEL	10 mg/kg bw per day (rat)

Summary

Value		Study	Safety factor
ARfD	0.1 mg/kg bw	Acute neurotoxicity, rat (supported by maternal toxicity in the developmental neurotoxicity rat study)	100

3. ACETOCHLOR

Source: ACETOCHLOR 79–185 JMPR 2015

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

In an acute neurotoxicity study in rats administered a single oral gavage acetochlor dose of 0, 150, 500 or 1500 mg/kg bw, decreased body weights and body weight gain and reduced feed consumption were observed at 1500 mg/kg bw. No neurotoxicity was observed.

In a 93-day study of neurotoxicity in rats given diets containing acetochlor at a concentration of 0, 200, 600 or 1750 ppm (equal to 0, 15.4, 47.6 and 139 mg/kg bw

per day for males and 0, 18.3, 55.9 and 166.5 mg/kg bw per day for females, respectively), marginal decreases in mean body weight and body weight gain in males and females were observed at 1750 ppm (equal to 139 mg/kg bw per day). There was no evidence for neurotoxicity or neuropathological effects up to 1750 ppm (equal to 139 mg/kg bw per day), the highest dose tested.

The Meeting concluded that acetochlor is not neurotoxic.

4. ACRINATHRIN

Source: EFSA Journal 2013;11(12):3469 8

Kind of Neurotoxicity: ACUTE NEUROTOXICITY EVIDENCE

Neurotoxicity was investigated in rats, showing an acute NOAEL of 1 mg/kg bw and a LOAEL of 2.4 mg/kg bw per day in a 90-day study.

Neurotoxicity was investigated in rats, showing an acute NOAEL of 1 mg/kg bw and a LOAEL of 2.4 mg/kg bw per day in a 90-day study.

Neurotoxicity was investigated in rats, showing an acute NOAEL of 1 mg/kg bw and a LOAEL of 2.4 mg/kg bw per day in a 90-day study.

For the derivation of the reference values, the experts agreed to use the results of the acute neurotoxicity study with rats. Applying a safety factor of 100, this resulted in an Acceptable Daily Intake (ADI) of 0.01 mg/kg bw per day, an Acute Reference Dose (ARfD) of 0.01 mg/kg bw and, considering an additional correction for an oral absorption of 71 %, an Acceptable Operator Exposure Level (AOEL) of 0.007 mg/kg bw per day.

5. ALDRIN / DIELDRIN / CHLORDANE / DDT / ENDRIN / HEPTACHLOR

Source: JMPR REPORT 1994

Kind of Neurotoxicity: NO DATA

TOXICOLOGICAL END-POINTS FOR PESTICIDES PRESENT IN THE ENVIRONMENT AS UNAVOIDABLE CONTAMINANTS

Several pesticides that have been allocated ADIs by the JMPR are no longer used in agricultural practice but may be present in food commodities as contaminants because of their persistence in the environment. Extraneous Residue Limits (ERLs) have been assigned to commodities containing these pesticides by the Codex

Committee on Pesticide Residues on the basis of food monitoring data, not Good Agricultural Practice.

ADIs were established in the past for these pesticides, most of which bioaccumulate in human tissues, on the basis of toxicological data, but studies with adequate power to detect toxic effects have not been performed on most of them. It is unlikely that further studies will be carried out, because these pesticides are no longer used in agricultural practice and do not have industrial sponsors. For these reasons, the Joint Meeting did not consider it appropriate to maintain traditional ADIs for them. At the same time, it is useful to maintain a numerical toxicological end-point to serve as a guideline with which potential dietary intakes can be compared.

For these reasons and to parallel the action that has been taken on residues, the Meeting converted the ADI for each of these pesticides to a provisional tolerable daily intake (PTDI).

The term "tolerable" rather than "acceptable" was used to signify permissibility rather than acceptability of the intake of environmental contaminants unavoidably associated with the consumption of otherwise wholesome food. Use of the term "provisional" expresses the fact that reliable data on the consequences of human exposure to these pesticides are lacking and that the submission from any source of relevant safety data is encouraged.

In line with the foregoing, PTDIs were established as follows:

Pesticide	**PTDI (mg/kg bw)**
aldrin/dieldrin	**0.0001**
chlordane	**0.0005**
DDT	**0.01**
endrin	**0.0002**
heptachlor	**0.0001**

The Meeting recommended that these PTDIs be reviewed whenever possible modifications of ERLs are considered.

6. ATRAZINE–DESETHYL (DEA)

Source: ATRAZINE 37–138 JMPR 2007

Kind of Neurotoxicity: NO EVIDENCE OF NEUROTOXICITY

No evidence of neurotoxicity in standard tests for toxicity; however, neuroendocrine mode of action has been established for atrazine and its chloro-s-triazine metabolites

Other toxicological studies:

Studies on metabolites DEA, DIA, DACT have the same neuroendocrine mode of action and similar potency to atrazine. Mode of neuroendocrine action Atrazine and its chlorometabolites modify hypothalamic catecholamine function and regulation, leading to alterations in pituitary LH and prolactin secretion.

Summary Atrazine

([a]Group ADI or ARfD for atrazine, deethyl-atrazine (DEA), deisopropyl-atrazine (DIA) and diaminochlorotriazine (DACT))

	Value	Study	Safety factor
Group ADI[a]	0–0.02 mg/kg bw	Sprague-Dawley rats; 6-month study of LH surge/estrous cycle disruption	100
Group ARfD[a]	0.1 mg/kg bw	Rat; special 4-day study of prolactin release, supported by studies of developmental toxicity in rats and rabbits	100

7. AZINPHOS-ETHYL

Source: JMPR

Kind of Neurotoxicity: NO DATA

1973 NO ADI

8. AZINPHOS-METHYL

Source: AZINPHOS-METHYL 139–172 JMPR 2007

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

Azinphos-methyl was highly acutely toxic (LD50 range, 4.4–26 mg/kg bw) when administered orally in an aqueous or non-aqueous vehicle to rats, and its profile of clinical signs was similar to those of other cholinesterase-inhibiting

organophosphorus pesticides. Clinical signs observed in experimental animals after acute exposure were salivation, lacrimation, vomiting, diarrhea, anorexia, reduced locomotor activity, piloerection, staggering gait and muscular tremors. These signs were generally evident within 5–20 min after dosing.

The main toxicological findings in repeat-dose studies in rodents and dogs were inhibition of cholinesterase activity and, at higher doses, reduced body-weight gain and signs of neurotoxicity. In long-term studies of toxicity, inhibition of **cholinesterase activity** was again **the main toxicological finding** in mice and rats.

The Meeting established an ADI of 0–0.03 mg/kg bw per day based on a NOAEL of 0.29 mg/kg bw per day for the absence of inhibition of erythrocyte acetylcholinesterase activity in a 30-day study of toxicity in male volunteers and a safety factor of 10. The Meeting also considered the ADI to be protective for other, non-neurotoxic effects of azinphos-methyl observed in short- and long-term studies with repeated doses, and in studies of reproductive and developmental toxicity, where the use of a safety factor of 10 would be appropriate.

The Meeting established an ARfD of 0.1 mg/kg bw based on the NOAEL of 1 mg/kg bw and using a safety factor of 10. In a study of acute neurotoxicity in rats, the NOAEL was 2 mg/kg bw on the basis of inhibition of cholinesterase activity in the brain. **At a dose of 2 mg/kg bw, significant inhibition of acetylcholinesterase activity in erythrocytes of male rats was observed, but not at 1 mg/kg bw in female rats.**

Estimate of acceptable daily intake for humans	0–0.03 mg/kg bw
Estimate of acute reference dose	0.1 mg/kg bw

9. AZOXYSTROBIN

Source: AZOXYSTROBIN 3–34 JMPR 2008

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

In a study of acute neurotoxicity in rats, no treatment-related effects on motor activity parameters, brain measurements (weight, length and width) or neurohistopathology were observed at doses of up to and including 2000 mg/kg bw.

In a short-term study of neurotoxicity in rats, no treatment-related changes in mortality, clinical signs, FOB, motor activity, brain measurements (weight, length, and

width), gross necropsy, or neurohistopathology were observed at doses of up to 2000 ppm, equal to 161 mg/kg bw per day, the highest dose tested.

Azoxystrobin was not considered to be neurotoxic on the basis of the available data.

The Meeting established an ADI of 0–0.2 mg/kg bw based on a NOAEL of 300 ppm (equal to 18.2 mg/kg bw per day) in a 2-year study of carcinogenicity in rats, identified on the basis of reduced body weights, food consumption and food efficiency, and bile-duct lesions seen at 750 ppm (equal to 34 mg/kg bw per day) and above, and using a safety factor of 100.

The Meeting concluded that it was unnecessary to establish an ARfD for azoxystrobin because no toxicity could be attributable to a single exposure in the available database, including a study of developmental toxicity in rats and rabbits and a study of acute neurotoxicity in rats.

Acute neurotoxicity	No sign of specific neurotoxicity

10. BHC (HCH or Benzene hexachloride)

Source: JMPR

Kind of Neurotoxicity: NO DATA

NO ADI	TECHNICAL GRADES; MIXTURES OF ISOMERS

11. BENALAXYL

Source: BENALAXYL 39–8 JMPR 2005

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Except for some nonspecific symptoms observed in the studies of acute toxicity at doses at or above the median lethal dose (LD50), the studies of acute toxicity and short- and long-term studies reported previously revealed neither clinical signs nor any biochemical or histopathological changes that might point to a neurotoxic potential of benalaxyl. Special studies in the field of neurotoxicity were therefore not necessary.

No specific studies of neurotoxicity with benalaxyl were available; however, no evidence of neurotoxicity was apparent from the available studies of toxicity.

The Meeting established an ADI of 0–0.07 mg/kg bw based on a NOAEL of 6.5 mg/kg bw per day for atrophy of the seminiferous tubules occurring at 25 mg/kg bw per day in a 1-year study in dogs and using a safety factor of 100.

The Meeting established a conservative ARfD of 0.1 mg/kg bw for benalaxyl for women of childbearing age on the basis of a NOAEL of 12.5 mg/kg bw per day in a study of developmental toxicity in rats, and a safety factor of 100. There is no concern regarding the acute toxicity of this compound for the rest of the population, including children.

Neurotoxicity/delayed neurotoxicity No specific study; no findings in other studies

12. BENOMYL

FAO Plant Production and Protection Paper, 133, 1996 - Pesticide residues in food - 1995. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment

Source: JMPR REPORT 1995

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

An ADI of 0-0.1 mg/kg bw was established on the basis of the NOAEL of 13 mg/kg bw per day in the two-year study in dogs and applying a safety factor of 100. This ADI should be used when assessing exposure to benomyl itself. Since the use of benomyl on crops gives rise to residues of carbendazim and since the ADI for carbendazim is lower than that which would be derived from the data on benomyl, the Meeting concluded that the intake of residues in food should be compared with the ADI of 0-0.03 mg/kg bw for carbendazim. A toxicological monograph was prepared, summarizing the data received since the previous evaluation and including summaries from the previous monograph and monograph addenda.

13. BIFENTHRIN

Source: BIFENTHRIN 3–52 JMPR 2009

Kind of Neurotoxicity: NEUROTOXICITY (SHORT-TERM/ACUTE)

In a study of acute neurotoxicity in rats given undiluted bifenthrin, the NOAEL was 35 mg/kg bw on the basis of mortality (females only), clinical signs and FOB findings and differences in motor activity observed at the LOAEL of 75 mg/kg bw. In a

published study by Wolansky, Gennings & Crofton (2006), male rats were given bifenthrin via gavage as nine doses (8–18 rats per dose) ranging from 0.03 to 28 mg/kg bw in corn oil (1 ml/kg bw), and motor activity was assessed for 1 h during the period of peak effects (4 h after dosing). The data were modelled, and a threshold dose was determined to be 1.28 mg/kg bw. The threshold dose is defined as an estimate of the highest no-effect level at which treated rats did not display any significant decreases in motor activity. In a 90-day study of neurotoxicity in rats, the NOAEL was 50 ppm, equal to 2.9 mg/kg bw per day, on the basis of neuromuscular findings (tremors, changes in grip strength and landing foot splay) observed at the LOAEL of 100 ppm, equal to 6.0 mg/kg bw per day. In a study of developmental neurotoxicity in rats given diets containing bifenthrin, the NOAEL for maternal toxicity was 50 ppm, equal to 3.6 mg/ kg bw per day, on the basis of tremors, clonic convulsions and increased grooming counts seen at the LOAEL of 100 ppm, equal to 7.2 mg/kg per day. The NOAEL for offspring toxicity was 50 ppm, equal to 3.6 mg/kg bw per day, on the basis of increased grooming counts seen at the LOAEL of 100 ppm, equal to 7.2 mg/kg bw per day. In studies of delayed neurotoxicity in adult hens and rats, no evidence of delayed neurotoxicity was observed.

On the basis of the available data, the Meeting considered that bifenthrin was neurotoxic.

The Meeting established an ADI of 0–0.01 mg/kg bw on the basis of a NOAEL of 1.0 mg/kg bw per day in a study of developmental toxicity in rats (gavage) based on the increased incidence of tremors in dams during days 10–19 of gestation and increased fetal and litter incidences of hydroureter without hydronephrosis seen at the LOAEL of 2.0 mg/kg bw per day, and using a safety factor of 100.

The Meeting established an acute reference dose (ARfD) of 0.01 mg/kg bw based on a threshold dose of 1.3 mg/kg bw for motor activity in a study of acute toxicity in rats treated by gavage and using a safety factor of 100.

Neurotoxicity/delayed neurotoxicity

Acute neurotoxicity Decrease in motor activity, (threshold dose) 1.28 mg/kg bw (rats)

Short-term study of neurotoxicity NOAEL: 2.9 mg/kg bw per day (rats)

Developmental neurotoxicity **No neurodevelopmental toxicity** observed, NOAEL: 125 ppm, equal to 9.0 mg/kg bw per day (rats), the highest dose tested

14. BOSCALID

Source: BOSCALID X-X JMPR 2006

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity No signs of neurotoxicity

In a single-dose study of neurotoxicity, no signs of neurotoxicity were observed.

In a multiple-dose study of neurotoxicity, there were no signs of neurotoxicity at any dose.

As there were no neurotoxic effects observed in any of the experiments with boscalid, studies on delayed neurotoxicity in hens were not performed.

In this study of developmental neurotoxicity, boscalid had no adverse effects on the embryonic, fetal and postnatal development of the nervous system in Wistar rats at doses of up to 10 000 ppm, equal to 1442 mg/kg bw per day, the highest dose tested (Kaufmann et al., 2001). The Meeting concluded that boscalid is not neurotoxic in adult or developing rats.

The Meeting concluded that boscalid is unlikely to cause neurotoxicity in human beings.

An ADI of 0–0.04 mg/kg bw was established for boscalid based on the NOAEL of 4.4 mg/kg bw per day, identified on the basis of increased gamma-glutamyltransferase activity and increased incidences of hepatic eosinophilic foci in male rats in a 24-month long-term dietary study of toxicity and carcinogenicity and a safety factor of 100.

The Meeting concluded that it was not necessary to establish an ARfD for boscalid in view of the well-demonstrated lack of toxicity in studies of acute toxicity, the absence of relevant developmental toxicity that could have occurred as a consequence of a single exposure, the absence of any indication of neurotoxicity and the absence of any other adverse effects that would be likely to be induced after a single or a small number of exposures in repeat-dose studies.

15. BROMOPROPYLATE

FAO Plant Production and Protection Paper, 122, 1993 - Pesticide residues in food - 1993. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues

Source: JMPR REPORT 1993

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

An ADI was established, based on the NOAEL of 2.7 mg/kg bw/day in the one-year study in dogs, using a 100-fold safety factor.

Estimate of acceptable daily intake for humans 0-0.03 mg/kg bw

16. BUPIRIMATE

Source: JMPR

Kind of Neurotoxicity: NO DATA

17. BUTRALIN

Reasoned opinion on the review of the existing maximum residue levels (MRLs) for butralin according to Article 12 of Regulation (EC) No 396/2005. EFSA Journal, Volume 10, Issue 4, April 2012, 2651 (EFSA Journal 2012;10(4):2651)

Source: EFSA

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

The toxicological profile of butralin was evaluated by France in the framework of Directive 91/414/EEC. Based on the available information, France proposed an ADI of 0.003 mg/kg bw/d (multigeneration study in the rat and teratogenicity study in the rabbit) and an ARfD of 0.003 mg/kg bw (multi-generation reproduction study in the rat). EFSA emphasizes that these toxicological reference values have never been peer reviewed, neither by Member States, nor by EFSA.

Considering that the use of butralin is no longer authorised within the EU, that no CXLs are available for this active substance and that no uses authorised in third countries were notified to the RMS, residues of butralin are not expected to occur in any plant commodity or livestock.

The nature of butralin residues in commodities of animal origin was also investigated in the lactating goats. Despite a high dosing rate, negligible residues were present in

the edible tissues and milk and it can be concluded that butralin would be by default the only marker for enforcement of a potential illegal use.

18. CADUSAFOS

Source: CADUSAFOS 53–102 JMPR 2009

Kind of Neurotoxicity: ACUTE NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity Organothiophosphorus compound, neurotoxic. No evidence of delayed neuropathy

Acute neurotoxicity Toxicity 0.02 mg/kg bw

In a 13-week feeding study of neurotoxicity in rats, the NOAEL was 0.5 ppm, equal to 0.031 mg/kg bw per day, on the basis of clinical signs, reduced body weights and reduced erythrocyte and brain cholinesterase activities at 300 ppm. **The Meeting considered that cadusafos is neurotoxic.**

In a study of delayed neurotoxicity in hens, the Meeting concluded that cadusafos is unlikely to cause delayed neuropathy at lethal doses.

The Meeting established an ADI of 0–0.0005 mg/kg bw based on a NOAEL of 1 ppm, equal to 0.045 mg/kg bw per day, identified on the basis of inhibition of erythrocyte cholinesterase activity at 5 ppm, equal to 0.222 mg/kg bw per day, in the long-term study in rats. A safety factor of 100 was applied.

The Meeting established an acute reference dose (ARfD) of 0.001 mg/kg bw based on a NOAEL of 0.1 mg/kg bw per day identified on the basis of clinical effects in dams at 0.3 mg/kg bw per day in the study of developmental toxicity in rabbits. A safety factor of 100 was applied. The large dose spacing between the LOAEL and the NOAEL in the study of acute neurotoxicity made this study unsuitable for the derivation of an ARfD. The Meeting also noted that the ARfD established might be conservative because it was derived using clinical signs that occurred only after administration of several doses.

19. CAPTAN

Source: CAPTAN 13–22 JMPR 2004

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

Other than developmental effects, captan produced no toxicological effects that might be considered to be a consequence of acute exposure. The Meeting concluded that it was not necessary to establish an ARfD for the general population, including children aged 1–6 years, for whom separate data on dietary intake are available. The Meeting concluded that it might be necessary to establish an ARfD to protect the embryo or fetus from possible effects in utero. Such an ARfD would apply to women of childbearing age.

The maternal toxicity and associated increases in skeletal variations and fetal bodyweight reductions observed in studies of developmental toxicity in rabbits are likely to be caused by high local concentrations of captan and are not considered to be relevant to dietary exposure. However, the observed intrauterine deaths and fetal malformations could not, with confidence, be attributed to maternal toxicity.

The Meeting concluded that the database was insufficient (in particular, with regard to the absence of studies on the developmental effects of THPI to establish the mode of action by which the increased incidences of intrauterine deaths and of fetuses with malformations, observed at 100mg/kgbw per day (NOAEL, 30mg/kgbw per day) in rabbits, were induced. As a consequence, their relevance for deriving an ARfD could not be dismissed. Therefore the Meeting established an ARfD of 0.3mg/kgbw, based on a NOAEL of 30mg/kgbw per day for increased incidences of intrauterine deaths and malformations at 100mg/kgbw per day in the study in rabbits and a safety factor of 100. The use of a safety factor of 100 was considered to be conservative; although the mode of action by which the developmental effects were induced is uncertain, they are possibly secondary to maternal toxicity. The ARfD also covers the effects observed in the case report in humans. The Meeting noted that it might be possible to refine the ARfD using the results of an appropriately designed study.

Estimate of acute reference dose 0.3mg/kgbw for women of childbearing age

Unnecessary for the general population.

20. CARBARYL

FAO Plant Production and Protection Paper, 167, 2001 - Pesticide residues in food - 2001. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group

Source: JMPR REPORT 2001

Kind of Neurotoxicity: ACUTE – SUBCHRONIC NEUROTOXICITY

Neurotoxicity / Delayed neurotoxicity

Acute; NOAEL < 10 mg/kg bw; inhibition of cholinesterase activity (rats, single dose) 3.8 mg/kg bw; inhibition of cholinesterase activity (5 weeks, dogs)

90-day; NOAEL 1 mg/kg bw per day; inhibition of cholinesterase activity (rats)

Delayed neuropathy Negative

21. CARBENDAZIM

Source: CARBENDAZIM 87–106 JMPR 2005

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

The Meeting established an ARfD of 0.1 mg/kg bw based on an overall NOAEL of 10 mg/kg bw per day for developmental toxicity from three studies in rats and one study in rabbits, and a safety factor of 100. The Meeting concluded that this ARfD applies only to women of childbearing age.

For the general population, including children, the Meeting established an ARfD of 0.5 mg/kg bw based on the NOAEL of 50 mg/kg bw in the study of toxicity to the male reproductive system in rats and supported by the studies on micronucleus or aneuploidy induction in vivo, using a safety factor of 100.

An additional safety factor for the severity of the effects was considered to be unnecessary, since the underlying mechanism is clearly understood and there is a clear threshold for these effects.

Estimate of acute reference dose 0.1 mg/kg bw for women of childbearing age 0.5 mg/kg bw for the general population, including children.

22. CARBOFURAN

Source: CARBOFURAN 81–104 JMPR 2008

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

Rat **Acute study of toxicity** (pups aged 11 days and adults) Inhibition of pup brain acetylcholinesterase activity 0.03 mg/kg bw

23. CHLORANTRANILIPROLE

Source: CHLORANTRANILIPROLE 105–134 JMPR 2008

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

In a study of acute neurotoxicity, no adverse compound-related effects on mortality, clinical signs of toxicity, body weight, bodyweight gain, food consumption, food efficiency, FOB parameters, motor activity, gross pathology, or neuropathology were observed at any dose in males or females. The NOAEL was 2000 mg/kg bw, the highest dose tested (Malley, 2004b).

In a 90-day study of neurotoxicity, there were no test substance-related effects on mortality, clinical observations, body weight, body-weight gain, food consumption, food efficiency, FOB parameters, motor activity, or on gross or microscopic pathology in males or females. The NOAEL was 20 000 ppm, equal to 1313 mg/kg bw per day, the highest dose tested (Malley, 2006b).

Therefore, regarding neurotoxicity studies, no neurotoxic effects were observed.

The Meeting established an acceptable daily intake (ADI) for chlorantraniliprole of 0–2 mg/kg bw on the basis of eosinophilic foci accompanied by hepatocellular hypertrophy and increased liver weight in mice in an 18-month feeding study for which the NOAEL was 158 mg/kg bw per day, and using a safety factor of 100.

The Meeting concluded that it was not necessary to establish an acute reference dose (ARfD) for chlorantraniliprole in view of its low acute toxicity, the absence of developmental toxicity, and the absence of any other toxicological effects that would be likely to be elicited by a single dose.

24. CHLORDANE (OXYCHLORDANE – TRANS-CHLORDANE)

Chlordane as undesirable substance in animal feed, EFSA Journal (2007) 582, 1-53

Source: EFSA REPORT

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

Chlordane has been banned for use in the European Union since 1981 and in most other countries world-wide. Chlordane was commercially introduced as a non-

systemic contact insecticide in 1947. From the 1970s a more refined formulation containing more than 95 % cis- and trans-chlordane was also produced.

Oxychlordane (a major metabolite of cis- and trans-chlordane) and nonachlor are more toxic than cis- and trans-chlordane. In mammals, the main target organs are the nervous system and the liver. Chlordane causes liver tumours in mice, probably via nongenotoxic mechanisms. Chlordane is classified by IARC as possibly carcinogenic to humans (group 2B).

JMPR re-evaluated its earlier assessments on chlordane in 1986 (FAO/WHO, 1987) and established an ADI of 0.5 µg/kg b.w. by applying an uncertainty factor of 100 to a NOAEL of 50 µg/kg b.w. per day for liver toxicity in a long-term study in rats. In 1994, JMPR converted the ADI into a provisional tolerable daily intake (PTDI) with the same value (FAO/WHO, 1995). Chlordane is not mutagenic in vivo and not or only weakly mutagenic in a few tests in vitro. It is a promoter of liver tumours in vivo and exhibit biochemical properties shared by many promoters of liver tumours.

The current human dietary exposure to chlordane is in the low ng/kg b.w. per day range, which is two to three orders of magnitude below the provisional tolerable daily intake of 500 ng/kg b.w. established by the WHO in 1995.

25. CHLORFENVINPHOS

FAO Plant Production and Protection Paper, 127, 1995 - Pesticide residues in food - 1994. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues.

Source: JMPR REPORT 1994

Kind of Neurotoxicity: NEUROTOXICITY EVIDENCE (SHORT-TERM)

WHO has classified chlorfenvinphos as extremely hazardous.

A four-week study in which mice were fed 0, 1, 10, 100 or 1000 ppm chlorfenvinphos in the diet showed inhibition of plasma and erythrocyte cholinesterase at 100 and 1000 ppm. Brain cholinesterase activity was inhibited at 10 and 1000 ppm in males and at all dose levels in females; hence no NOAEL could be established for female mice (NOAEL <0.18 mg/kg bw per day) and the NOAEL in males was 1 ppm, equal to 0.18 mg/kg bw per day.

In a one-year study in which dogs were fed 0, 3, 100 or 3000 ppm in the diet, inhibition of erythrocyte cholinesterase activity and increased relative adrenal weight

were seen in males and increased relative thyroid weight in females at the highest dose. The NOAEL was 100 ppm, equal to 2.8 mg/kg bw per day.

Delayed neurotoxicity in chickens has not been evaluated.

An ADI of 0-0.0005 mg/kg bw was established on the basis of the NOAEL of 0.05 mg/kg bw per day in the two-generation reproductive toxicity study in rats and a 100-fold safety factor.

26. CHLORMEQUAT

FAO Plant Production and Protection Paper, 153, 1999 - Pesticide residues in food - 1999. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group

Source: JMPR REPORT 1999

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

The compound was reviewed again by the 1997 Meeting, when an ADI of 0-0.05 mg/kg bw was allocated on the basis of the NOAEL of 4.7 mg/kg bw per day for diarrhoea, vomiting, and salivation in a one-year study of toxicity in dogs, and using a safety factor of 100. The compound was considered by the present Meeting solely to determine an acute reference dose.

An acute reference dose of 0.05 mg/kg bw was established on the basis of the NOAEL of 4.7 mg/kg bw per day in the one-year study in dogs, as the clinical signs that were found were considered to be acute. A 100-fold safety factor was used.

27. CHLOROTHALONIL

Source: CHLOROTHALONIL 103–154 JMPR 2009

Kind of Neurotoxicity: NO NEUROTOXICITY DATA / NO NEUROTOXIC POTENTIAL

Neurotoxicity No data.

No indication of neurotoxic potential.

28. CHLORPROFAM

Source: CHLORPROPHAM - JMPR 2005.pdf

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

29. CHLORPYRIFOS

FAO Plant Production and Protection Paper, 153, 1999 - Pesticide residues in food - 1999. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group

Source: JMPR REPORT 1999

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

30. CHLORPYRIFOS-METHYL

Source: CHLORPYRIFOS-METHYL 155–202 JMPR 2009

Kind of Neurotoxicity: DELAYED NEUROPATHY EVIDENCE

No acute or repeated-dose neurotoxicity studies or developmental neurotoxicity studies have been performed with chlorpyrifos-methyl.

The Meeting concluded that chlorpyrifos-methyl **was unlikely** to produce delayed neuropathy in the absence of very severe cholinergic toxicity.

Histopathological indications of neuropathy at 5000 mg/kg bw; no indications of delayed neuropathy at 500 mg/kg bw per day for 13 weeks; very weak inhibitor of NTE in vitro.

31. CLOTHIANIDIN

Source: CLOTHIANIDIN 19–116 JMPR 2010

Kind of Neurotoxicity: ACUTE/SHORT TERM NEUROTOXICITY

The Meeting concluded that clothianidin is not a developmental neurotoxicant. At relatively high doses, it can cause transient, acute neurobehavioural effects.

Neurotoxicity/delayed neurotoxicity:

Acute neurotoxicity target/critical effect	**Decreased locomotor activity**
Lowest relevant acute neurotoxic NOAEL	60 mg/kg bw per day
Short-term neurotoxicity target/critical effect	Decreased body weight and feed consumption

Lowest relevant subchronic neurotoxic NOAEL	60 mg/kg bw per day
Developmental neurotoxicity target/critical effect	No biologically significant effects
Lowest relevant developmental neurotoxic NOAEL	142 mg/kg bw per day (highest dose tested)

32. COUMAPHOS

Source: JMPR

Kind of Neurotoxicity: NO DATA

NO ADI

33. CYFLUTHRIN

Source: CYFLUTHRIN AND BETA-CYFLUTHRIN X-X JMPR 2006

Kind of Neurotoxicity: ACUTE NEUROTOXICITY EVIDENCE

Acute neurotoxicity	Neurotoxicity 1 mg/kg bw → ARfD established

Neurotoxicity/delayed neurotoxicity:

Neurotoxicity	Behavioural effects (increased motility, grooming and digging movements)
Lowest relevant oral NOAEL	1 mg/kg bw (single and repeated dose by gavage, beta-cyfl uthrin and cyfluthrin, rats)

34. CYHALOTHRIN / LAMBDA-CYHALOTHRIN

Source: LAMBDA-CYHALOTHRIN 173–200 JMPR 2007

Kind of Neurotoxicity: ACUTE NEUROTOXICITY EVIDENCE

Neurotoxicity	Type II pyrethroid toxicity (choreoathetosis/salivation syndrome)

No evidence for developmental neurotoxicity was observed.

The most sensitive systemic effect of lambda-cyhalothrin/cyhalothrin was neurotoxicity (decreased motor activity), which was observed in a study of acute toxicity in rats. On the basis of these effects, the Meeting established a group ADI for cyhalothrin and lambda cyhalothrin of 0–0.02 mg/kg bw, using a safety factor of 25.

The Meeting established a group ARfD for cyhalothrin and lambda-cyhalothrin of 0.02 mg/kg bw on the basis of systemic neurotoxicity (decreased motor activity) observed in a study of acute toxicity in rats.

35. CYPERMETHRIN

Source: CYPERMETHRINS X-X JMPR 2006

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

GROUP ADI FOR CYPERMETHRIN, ALPHA-CYPERMETHRIN AND ZETA-CYPERMETHRIN

Neurotoxicity:

Target/critical effect	Clinical signs, changes in FOB tests and degenerative changes to the sciatic nerve
Lowest relevant NOAEL	4 mg/kg bw per day (single-dose study in rats)
Delayed neurotoxicity:	
Target/critical effect	No delayed effect
Lowest relevant NOAEL	> 1000 mg/kg bw per day (hens)
Medical data	Paraesthesia after dermal exposure
Group ARfD 0.04 mg/kg bw cypermethrin (& cypermethrin)	Rat, study of acute neurotoxicity with alpha-100

36. CYPROCONAZOLE

Source: CYPROCONAZOLE 117–202 JMPR 2010

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Subchronic neurotoxicity	Not neurotoxic (90-day study in rats)

37. CYPRODINIL

Source: CYPRODINIL 33–84 JMPR 2003

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Lack of neurotoxicity after a single exposure

Neurotoxicity/delayed neurotoxicity

Acute neurotoxicity	No evidence of neuropathology at doses of up to 2000 mg/kgbw in rats; NOAEL was 200 mg/kg bw, on the basis of clinical signs
90-day study of neurotoxicity	No evidence of neurotoxicity or neuropathology; NOAEL was 54.5 mg/kg bw per day on the basis of liver, kidney and thyroid histopathology

38. CYROMAZINE

Source: CYROMAZINE X-X JMPR 2006

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

Neurotoxicity/delayed neurotoxicity	No specific study; no findings in other studies

39. DDT /DDD/ DDE

FAO Plant Production and Protection Paper, 163, 2001 - Pesticide residues in food 2000 Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group. CONFIRMED ALSO BY 2002 JMPR.

Source: JMPR REPORTS 2000 & 2002

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

An ADI of 0–0.02 mg/kg bw was allocated in 1984 for any combination of DDT, DDD, and DDE on the basis of data for both humans and experimental animals. The 1994 JMPR converted the ADI to a PTDI. An extensive range of studies on the biochemistry and toxicology of DDT and related compounds, including hormone-modulating effects, in vivo and in vitro has been reported since the 1984 JMPR. The present Meeting considered numerous reviews of the toxicity of DDT that have been published recently, and summarized new data on the toxicologically relevant effects of DDT and its metabolites. Mixtures of the para,para' and ortho,para' isomers of DDT, DDE, and TDE are referred to as the ‘DDT complex’.

The newer studies and reviews provided the basis for a change by the present Meeting of the PTDI established in 1984. **The Meeting derived a PDTI of 0.01 mg/kg bw on the basis of the NOAEL of 1 mg/kg bw per day for developmental toxicity in rats and a safety factor of 100. DDT is no longer used in agricultural practice but may be present in food commodities as a contaminant because of**

its persistence in the environment. As peaks of acute dietary intake above the PTDI are not likely to occur, an acute RfD was not allocated.

40. DELTAMETHRIN

FAO Plant Production and Protection Paper, 163, 2001 - Pesticide residues in food - 2000. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group

Source: JMPR REPORT 2000

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

The results of acute and 90-day studies of neurotoxicity in rats and of acute delayed

Neurotoxicity in hens **showed that deltamethrin does not induce neuropathological changes.** The **NOAEL for neurotoxicity** in a study in rats given a single dose by gavage was 5 mg/kg bw **on the basis of effects in a battery of tests for function and locomotor activity at 15 mg/kg bw per day**. The NOAEL for systemic toxicity and neurotoxicity in a 90-day study in rats was 200 ppm, equal to 14 mg/kg bw per day, on the basis of effects on function in a battery of tests at 800 ppm, equal to 54 mg/kg bw per day, the highest dose tested.

The Meeting concluded that the existing database was adequate to characterize the potential hazard of deltamethrin to fetuses, infants, and children. Although **deltamethrin is known to be neurotoxic to adults**, the Meeting did not recommend that a study of developmental neurotoxicity be conducted since there was no evidence that offspring exposed pre- or postnatally are more sensitive than adults in the same experiment.

Neurotoxicity/Delayed neurotoxicity		NOAEL, 5 mg/kg bw per day in a single-dose study in rats	
		NOAEL, 14 mg/kg bw per day in a 90-day study in rats; **no delayed effect**	
		NOAEL > 5000 mg/kg bw per day in hens	
Acute RfD:	**0.05 mg/kg bw**	**Study of acute neurotoxicity in rats**	**100**

41. OXYDEMETON-METHYL

Source: OXYDEMETON-METHYL 283-298 JMPR 2002

Kind of Neurotoxicity: ACUTE & SHORT-TERM NEUROTOXICITY

Acute and short-term neurotoxicity observed.

42. DIAZINON

Source: DIAZINON X-X JMPR 2006

Kind of Neurotoxicity: ACUTE-SUBCHRONIC-CHRONIC NEUROTOXICITY

The most sensitive end-point observed in all species given single and repeated doses of diazinon was inhibition of cholinesterase activity. This apparent sex difference in sensitivity for cholinesterase inhibition was confirmed in a 28-day dietary exposure study in rats in which cholinesterase activity was monitored in the blood and in regional areas of the brain.

In a 1-year study in dogs, clinical signs and reduced body-weight gain were observed in females at slightly lower doses.

The Meeting reaffirmed the ARfD of 0.03 mg/kg bw established by the 2001 JMPR. This ARfD was based on the NOAEL of 2.5 mg/kg bw identified in studies of acute toxicity and neurotoxicity in rats, and a safety factor of 100. This ARfD was supported by the NOAEL of 0.21 mg/kg bw identified in the study in humans given a single dose of diazinon, and a safety factor of 10.

43. DICHLORVOS

Source: DICHLORVOS (addendum) 93–150 JMPR 2011

Kind of Neurotoxicity: ACUTE – SUBCHRONIC NEUROTOXICITY

Neurotoxicity	Neurotoxic due to cholinesterase inhibition. No evidence of delayed neuropathy up to 16.5 mg/kg bw (hens) or 70 mg/kg bw (rats), the highest doses tested. Very weak inhibitor of NTE activity in vitro
Lowest relevant oral NOAEL	0.1 mg/kg bw per day (13-week rat study)
Developmental neurotoxicity	No evidence of developmental neurotoxicity up to 7.5 mg/kg bw per day (rats), highest dose tested

In studies of neurotoxicity in rats, dichlorvos was administered as a single dose of up to 70 mg/kg bw or as repeated doses of up to 15 mg/kg bw per day. The NOAEL following a single gavage dose was 0.5 mg/kg bw, based on clinical signs of neurotoxicity at 35 mg/kg bw observed during the functional observational battery 15 minutes after dosing; no signs of neurotoxicity were observed 7 or 14 days after dosing. Following repeated gavage doses of up to 15 mg/kg bw per day for 13 weeks, clinical signs of neurotoxicity were observed within 15 minutes of dosing throughout the study, at and above 7.5 mg/kg bw per day. These signs coincided with the inhibition of ChE activity in erythrocytes and brain.

44. DICOFOL

Source: DICOFOL (addendum) 151–210 JMPR 2011

Kind of Neurotoxicity: ACUTE – SUBCHRONIC NEUROTOXICITY

Acute neurotoxicity target/critical effect	Ataxia, decreased motor activity at systemically toxic dose
Lowest relevant acute neurotoxicity NOAEL	15 mg/kg bw
Subchronic neurotoxicity target/critical effect	Decreased motor activity at systemically toxic doses
Lowest relevant subchronic neurotoxicity NOAEL	0.2 mg/kg bw per day (90-day neurotoxicity study)

45. DIETHOFENCARB

Source: JMPR

Kind of Neurotoxicity: NO DATA

46. DIFENOCONAZOLE

Source: DIFENOCONAZOLE 201–272 JMPR 2007

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

The Meeting concluded that difenoconazole is unlikely to cause neurotoxicity in humans.

Neurotoxicity/delayed neurotoxicity:

Single-dose study of neurotoxicity	No signs of neurotoxicity, NOAEL was 25 mg/kg bw (rats)
Ninety-day study of neurotoxicity	No signs of neurotoxicity, NOAEL was 2.3 mg/kg bw (rats)

These responses were considered to be non-specific effects of difenoconazole because of the absence of any changes in the multiple end-points of neurotoxicity that were measured and the absence of neuropathological findings.

An acute reference dose (ARfD) of 0.3 mg/kg bw was established for difenoconazole. This was based on the NOAEL of 25.0 mg/kg bw in rats, identified on the basis of clinical signs in a singledose study of neurotoxicity and using a safety factor of 100. This ARfD is supported by the NOAEL of 25 mg/kg bw per day for maternal toxicity in a study of developmental toxicity in rats and rabbits on the basis of excess salivation in rats at 100 mg/kg bw per day and body-weight loss in rabbits d uring the first few days of treatment at 75 mg/kg bw per day.

47. DIMETHOATE

Source: DIMETHOATE 85–100 JMPR 2003

Kind of Neurotoxicity: ACUTE/SUBCHRONIC/CHRONIC/DNT

After considering the previous evaluations of dimethoate and the new data submitted, the Meeting established an acute RfD of 0.02mg/kgbw on the basis of the overall NOAEL of 2mg/kgbw for cholinesterase inhibition in studies in rats, and a safety factor of 100. This acute RfD was supported by the NOAEL of about 0.2mg/kgbw per day in studies in volunteers receiving single or repeated doses, which were evaluated by the 1996 JMPR.

The Meeting considered these effects to be of no relevance for setting the acute RfD, since they would not be expected to occur after a single exposure, and concluded that the new studies supported the current ADI of 0–0.002mg/kgbw.

48. DIMETHOMORPH

Source: DIMETHOMORPH 273–315 JMPR 2007

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity	No evidence in conventional studies

49. DIPHENYLAMINE

FAO Plant Production and Protection Paper, 148, 1999 - Pesticide residues in food - 1998. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group

Source: JMPR 1998

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

Neurotoxicity / Delayed neurotoxicity	No data

50. ENDOSULFAN

Source: JMPR 1998

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

FAO Plant Production and Protection Paper, 148, 1999 - Pesticide residues in food - 1998. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group

Acute reference dose	**0.02 mg/kg bw based on a NOAEL of 2 mg/kg bw per day in rats in a study of neurotoxicity and with a safety factor of 100**

51. ENDOSULFAN I (ALPHA) & ENDOSULFAN II (BETA)

Source: JMPR

Kind of Neurotoxicity: NO DATA

52. ENDOSULFAN SULFATE

Source: JMPR REPORT 1998

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

The metabolites of endosulfan include endosulfan sulfate, diol, hydroxy-ether, ether, and lactone but most of its metabolites are polar substances which have not yet been identified. Endosulfan would not be expected to accumulate significantly in human tissues. (JMPR REPORT 1998)

53. EPOXICONAZOLE

Source: JMPR

Kind of Neurotoxicity: NO DATA

54. ESFENVALERATE

Source: ESFENVALERATE 41-76 JMPR 2002

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

Target /Critical effect	Tremors
Lowest relevant NOAEL for acute neurotoxicity	**1.8 mg/kg bw**
Target /Critical effect for 90-day neurotoxicity	Decreased motoractivity
Lowest relevant NOAEL for 90-day neurotoxicity	**3.0 mg/kg bw**

Acute RfD 0.02 mg/kg bw Rat, acute neurotoxicity 100

55. ETHION

Source: JMPR

Kind of Neurotoxicity: NO DATA

56. ETHOPROPHOS

FAO Plant Production and Protection Paper, 153, 1999 - Pesticide residues in food - 1999. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group.

Source: JMPR REPORT 1999

Kind of Neurotoxicity: ACUTE-CHRONIC NEUROTOXICITY

Neurotoxicity/ Delayed neurotoxicity	5 mg/kg bw per day (acute study in rats) <4 ppm, equal to 0.26 mg/kg bw per day (13-week study in rats) **No evidence for delayed neurotoxicity** in hens, but some equivocal findings.

ADI 0-0.0004 mg/kg bw Two-year study, rat; two-generation study of reproductive toxicity, rats 100

Acute reference dose 0.05 mg/kg bw Acute neurotoxicity, rats 100

The present Meeting established an **ADI** of 0-0.0004 mg/kg bw on the basis of the NOAEL of 1 ppm, equal to 0.04 mg/kg bw per day, **for inhibition of brain acetylcholinesterase activity in the two-year study of toxicity and** carcinogenicity in rats and in the study of reproductive toxicity in rats, and a 100-fold safety factor.

An **acute reference dose** of 0.05 mg/kg bw was established on the **basis** of the NOAEL of 5 mg/kg bw **in the study of acute neurotoxicity in rats**, in which functional and/or behavioural effects and inhibition of erythrocyte acetylcholinesterase were observed at the next highest dose, and a 100-fold safety factor.

57. ETOFENPROX

Source: ETOFENPROX 253–324 JMPR 2011

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity	Acute neurotoxicity Not neurotoxic (rats)
Subacute neurotoxicity	Not neurotoxic (13-week study in rats)
Neurodevelopmental toxicity	Not neurodevelopmental toxicant (rats)

58. FAMOXADONE

Source: FAMOXADONE 101–149 JMPR 2003

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity

Target/critical effect	None
Lowest relevant NOAEL	>1000mg/kgbw

59. FENARIMOL

FAO Plant Production and Protection Paper, 133, 1996 - Pesticide residues in food - 1995. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment

Source: JMPR REPORT 1995

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

A toxicological monograph was prepared, summarizing the data that were reviewed by the present Meeting.

TOXICOLOGICAL EVALUATION

Levels that cause no toxic effect

Mouse: 24 mg/kg bw per day (12-month study of chronic toxicity) 20 mg/kg bw per day (three-generation study of reproductive toxicity)

Rat: 1.2 mg/kg bw per day (three studies of carcinogenicity) 0.62 mg/kg bw per day (multigeneration study of reproductive toxicity)* 13 mg/kg bw per day (embryo- and fetotoxicity in study of developmental toxicity)

Dog: 12 mg/kg bw per day (one-year study of toxicity)

Rabbit: 50 mg/kg bw per day (maternal and embryo- or fetotoxicity in a study of developmental toxicity)

*Data considered irrelevant for evaluation with respect to human health.

Estimate of acceptable daily intake for humans 0-0.01 mg/kg bw

60. FENHEXAMID

Source: FENHEXAMID 255–301 JMPR 2005

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity

Acute neurotoxicity	No evidence of neurotoxicity at doses of up to 2000 mg/kg bw (rats)

61. FENITROTHION

FAO Plant Production and Protection Paper, 163, 2001 - Pesticide residues in food - 2000. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group

Source: JMPR REPORT 2000

Kind of Neurotoxicity: REVERSIBLE NEUROTOXICITY EVIDENCE

Neurotoxicity/Delayed neurotoxicity	Reversible neurotoxicity consistent with cholinesterase inhibition. No evidence of delayed neurotoxicity or of histopathological changes in nerves of hens (500 mg/kg bw) or rats (200 mg/kg bw or 17.6 mg/kg bw per day for 13 weeks)

The Meeting affirmed the **ADI** of 0–0.005 mg/kg bw that was established by the 1988 Joint Meeting, which was based on a NOAEL of 0.5 mg/kg bw per day for inhibition of brain and erythrocyte cholinesterase activity in a 2-year study of toxicity in rats and a safety factor of 100. This was supported by a **NOAEL of 0.57 mg/kg bw per day for inhibition of brain and Erythrocyte cholinesterase activity in a 3-month study of ocular toxicity in rats and** a NOAEL of 0.65 mg/kg bw per day for reduced food consumption and body-weight gain in a study of reproductive toxicity in rats. The 4-day study in volunteers was not considered suitable for establishing an ADI because of its short duration and the associated absence of steady-state kinetics.

The Meeting allocated an **acute RfD of 0.04 mg/kg bw** to fenitrothion on the basis of a NOAEL of 0.36 mg/kg bw for inhibition of erythrocyte acetylcholinesterase activity in a study in volunteers and a safety factor of 10.

62. FENOXYCARB

Source: JMPR

Kind of Neurotoxicity: NO DATA

63. FENPROPIDINE

Source: JMPR

Kind of Neurotoxicity: NO DATA

64. FENPROPIMORPH

Source: FENPROPIMORPH 27–34 JMPR 2004

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

In a study of acute neurotoxicity in rats, the NOAEL was 100mg/kgbw per day on the basis of clinical and behavioural signs observed at doses of 500 and 1500mg/kgbw per day.

65. FENTHION

FAO Plant Production and Protection Paper, 145, 1998 - Pesticide residues in food - 1997. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group.

Source: JMPR REPORT 1997

Kind of Neurotoxicity: ACUTE NEUROTOXICITY EVIDENCE

Fenthion was reviewed by **the 1995 JMPR**, which established an **ADI of 0-0.007 mg/kg bw** on the basis of an NOAEL of 0.07 mg/kg bw per day (the highest dose tested) for the inhibition of erythrocyte acetylcholinesterase activity in a 25-day study in volunteers. The available data did not permit the Meeting to establish an acute reference dose (acute RfD) different from the ADI. A study of neurotoxicity in rats given a single dose was available to the present Meeting to assist in reviewing the acute RfD.

In rats treated by gavage with **single doses** of 0, 1, **50** (males), **75** (females), **150** (males), or 225 (females) mg/kg bw of technical-grade fenthion, **the NOAEL for the inhibition of brain acetylcholinesterase activity and for neurobehavioural effects was 1 mg/kg bw.**

In a study that was reviewed by the 1995 JMPR, the administration of 0.07 mg/kg bw to volunteers daily for about 25 days did not inhibit erythrocyte acetylcholinesterase activity.

The Meeting concluded that an **acute reference dose of 0.01 mg/kg bw** could be allocated by taking into account the NOAEL of 1 mg/kg bw in rats and applying a safety factor of 100.

An addendum to the toxicological monograph was prepared.

TOXICOLOGICAL EVALUATION RELEVANT FOR ESTABLISHING AN **ACUTE RFD**

Levels that cause no toxic effect

Rat: 1 mg/kg bw (single oral administration, inhibition of brain acetylcholinesterase activity)

Human: 0.07 mg /kg bw per day (four-week study in volunteers, highest dose tested)

Estimated acute reference dose for humans 0.01 mg/kg bw

66. FENTHION OXON

Source: JMPR

Kind of Neurotoxicity: NO DATA

67. FENTHION SULFONE

Source: JMPR

Kind of Neurotoxicity: NO DATA

68. FENTHION SULFOXIDE

Source: JMPR

Kind of Neurotoxicity: NO DATA

69. FENVALERATE

Source: FENVALERATE 307–361 JMPR 2012

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

Neurotoxicity Target/**critical effect**	**Clinical signs** typical of type II pyrethroids
Acute neurotoxicity NOAEL	20 mg/kg bw (rat)
Subchronic neurotoxicity	No data

A study of the **neurotoxic potential** of **esfenvalerate and fenvalerate** in corn oil was conducted in rats following a **single** oral gavage **dose**. The NOAELs were 5 and

20 mg/kg bw for esfenvalerate and fenvalerate, respectively, based on the toxic signs typical of type II pyrethroids. **Signs were observed within 2 hours of dosing** at 20 and 90 mg/kg bw **for esfenvalerate and fenvalerate, respectively.**

No histopathological lesions in the sciatic nerve were observed in rats following a single-dose administration of fenvalerate at 200 mg/kg bw. In a separate study, rats were administered fenvalerate orally at dose levels ranging from 0 to 400 mg/kg bw per day for 7 consecutive days. A significant neurological deficit was demonstrated using an inclined plane test (expressed as the angle at which the animals cannot maintain their hold on an inclining plane). In addition to functional deficits, increases in the activity of the lysosomal enzymes β-glucuronidase and β-galactosidase in the posterior tibial nerve and trigeminal ganglia were observed.

70. FIPRONIL

FAO Plant Production and Protection Paper, 145, 1998 - Pesticide residues in food - 1997. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group.

Source: JMPR REPORT 1997

Kind of Neurotoxicity: SHORT TERM-DNT NEUROTOXICITY

Acute reference dose for fipronil:

The Meeting allocated an acute reference dose of 0.003 mg/kg bw for both fipronil and fipronildesulfinyl on the basis of the NOAEL of 0.3 mg/kg bw per day in a study of neurotoxicity in rats given repeated doses of fipronil, and a safety factor of 100. The study of neurotoxicity in rats given single doses was not considered in allocating the acute reference dose because of concern about the prolonged toxicokinetics of fipronil. This acute reference dose will provide a safety factor of about 700 for the NOAEL in the study of neurotoxicity in rats given single doses of fipronil-desulfinyl.

Studies without which the determination of an ADI is impracticable, to be provided by 2000:

1. Short-term study of neurotoxicity in rats with fipronil-desulfinyl in the diet.

2. Developmental neurotoxicity study in rats with fipronil-desulfinyl in the diet.

3. The results of an ongoing long-term study with fipronil-desulfinyl in rats.

Toxicological criteria for setting guidance values for dietary and non-dietary exposure to fipronil and its photodegradation product fipronil-desulfinyl:

SHORT-TERM (1-7days):

Neurotoxicity, rat (**single dose** by gavage)	**NOAEL** = 0.5 mg/kg bw per day: **decreased hind-leg splay**
Medium term (1-26 weeks)	
Repeated oral, **developmental**	
neurotoxicity, rat	NOAEL = 0.9 mg/kg bw per day for maternal toxicity.
	NOAEL = 0.05 mg/kg bw per day for **developmental toxicity**.

Levels that cause **no toxic effect:**

RAT:

0.5 mg/kg bw (single dose, study of neurotoxicity by gavage)

5 ppm, equal to 0.3 mg/kg bw per day (repeated doses in the diet, study of neurotoxicity)

10 ppm, equal to 0.9 mg/kg bw per day (maternal toxicity and developmental neurotoxicity in a study of developmental neurotoxicity)

0.5 ppm, equal to 0.05 mg/kg bw per day (developmental toxicity in a study of developmental neurotoxicity)

71. FLONICAMID

Source: FLONICAMID X–X JMPR 2015

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity:

Acute neurotoxicity NOAEL	600 mg/kg bw (highest dose tested; rat)
Subchronic neurotoxicity NOAEL	625 mg/kg bw per day (highest dose tested; rat)
Developmental neurotoxicity NOAEL	No data

The Meeting concluded that it **was not necessary to establish an acute reference dose** (ARfD) for flonicamid in view of its low acute toxicity and the absence of developmental toxicity and any other toxicological effects that would be likely to be elicited by a single dose.

The Meeting established an ADI of 0–0.07 mg/kg bw on the basis of a NOAEL of 7.32 mg/kg bw per day in the 2-year rat study, based on decreased body weight, decreased rearing, effects on clinical chemistry and effects on kidney and muscle observed at 36.5 mg/kg bw per day. This ADI is supported by the overall NOAEL of 8 mg/kg bw per day in dogs and the NOAELs of 7.5 mg/kg bw per day for maternal and embryo/fetal toxicity in the developmental toxicity study in rabbits. A safety factor of 100 was applied.

72. FLUDIOXONIL

Source: FLUDIOXONIL 47–84 JMPR 2004

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity No evidence of neurotoxicity or delayed neurotoxicity in any study conducted

73. FLUBENDIAMIDE

Source: FLUBENDIAMIDE 345–382 JMPR 2010

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity

Neurotoxicity	No neurotoxic effects
Developmental neurotoxicity	No neurotoxic effects

74. FLUOPICOLIDE

Source: FLUOPICOLIDE 269–356 JMPR 2009

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity	No signs of neurotoxicity	No data

75. FLUSILAZOLE

Source: FLUSILAZOLE 317–347 JMPR 2007

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

No neurotoxic effects were seen during conventional repeat-dose studies with flusilazole.

Neurotoxicity/delayed neurotoxicity:

No indications of neurotoxicity in studies of acute toxicity or repeated doses

ADI 0–0.007 mg/kg bw	Dog, 1-year study	100
ARfD 0.02 mg/kg bw	Rat, study of developmental toxicity	100

76. FLUTRIAFOL

Source: FLUTRIAFOL 325–372 JMPR 2011

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

Neurotoxicity/delayed neurotoxicity

Acute study	Altered FOB and motor activity; **neurotoxicity** NOAEL 250 mg/kg bw (rat)
Ninety-day study	**Not neurotoxic**

In an acute neurotoxicity study in rats, there was no evidence of neuropathy at 750 mg/kg bw, the highest dose tested. The NOAEL for acute neurotoxicity was 250 mg/kg bw, based on altered FOB and motor activity findings on day 1 at 750 mg/kg bw. The NOAEL for general toxicity was less than 125 mg/kg bw, based on transient reductions in body weight gain in males at all doses. In a repeated-dose neurotoxicity study, there were no signs of neuropathy or neurotoxicity at 3000 ppm (equal to 172 mg/kg bw per day), the highest dose tested.

77. FLUVALINATE

Source: JMPR

Kind of Neurotoxicity: NO DATA

78. FOLPET

Source: FOLPET 85–94 JMPR 2004

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Other than developmental effects, folpet produced no toxicological effects that might be considered to be a consequence of acute exposure. The Meeting concluded that it was not necessary to establish an ARfD for the general population, including children aged 1–6 years for whom separate data on dietary intake are available. The Meeting concluded that it might be necessary to establish an ARfD to protect the embryo or fetus from possible effects in utero. Such an ARfD would apply to women of childbearing age.

The maternal toxicity and the associated reductions in fetal body weight, delayed ossification and increased incidences in skeletal variations observed in studies of developmental toxicity in rabbits are likely to be caused by high local concentrations of folpet and are not considered to be relevant to dietary exposure. However, the increased incidence of hydrocephalus observed could not be attributed with confidence to maternal toxicity.

The Meeting concluded that the database was insufficient (in particular, with regard to the absence of studies on the developmental effects of phthalimide) to establish the mode of action by which the increased incidence of hydrocephalus, observed in rabbits at 60mg/kg bw per day (NOAEL, 20mg/kg bw per day) was induced, and as a consequence, their relevance for deriving an ARfD could not be dismissed. Therefore the Meeting established an ARfD of 0.2mg/kg bw based on a NOAEL of 20mg/kg bw per day for the increased incidence of hydrocephalus at 60mg/kg bw per day in rabbits and a safety factor of 100. The use of a safety factor of 100 was considered to be conservative; although the mode of action by which the developmental effects are induced was uncertain, they are possibly secondary to maternal toxicity. The Meeting noted that it might be possible to refine this ARfD using the results of an appropriately designed study.

Estimate of acute reference dose

0.2mg/kg bw for women of childbearing age

Unnecessary for the general population

79. FORMETANATE

Source: JMPR

Kind of Neurotoxicity: NO DATA

80. GLYPHOSATE

Source: GLYPHOSATE 95–169 JMPR 2004

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity	No evidence of neurotoxicty in any study conducted

81. HEPTACHLOR and its metabolites

Source: JMPR REPORT 1991

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

82. HEXACHLOROBENZENE / HCB

Source: JMPR

Kind of Neurotoxicity: NO DATA

ADI WITHDRAWN IN 1978

83. HCH

Source: JMPR

Kind of Neurotoxicity: NO DATA

84. IMAZALIL

Source: IMAZALIL 303–314 JMPR 2005

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Special studies: developmental neurotoxicity

A study of reproductive toxicity with measurement of neurobehavioural end-points was reported in which groups of 10 male and 10 female Crj.

In view of the inconsistent results at the lowest dose, the many end-points measured, and lack of dose–response relationships in the adverse outcomes observed, the NOAEL was the lowest dose tested, about 20 mg/kg bw per day (Tanaka, 1995).

85. IMIDACLOPRID

FAO Plant Production and Protection Paper, 167, 2001 - Pesticide residues in food - 2001. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group.

Source: JMPR REPORT 2001

Kind of Neurotoxicity: ACUTE – SHORT TERM NEUROTOXICITY

In a study of acute neurotoxicity in rats, clinical signs and effects on motor and locomotor activity and in the “functional observational battery” were observed at doses 150 mg/kg bw 1 day after application. Complete recovery was observed within 7 days. The NOAEL was 42 mg/kg bw. In a 13-week study of neurotoxicity in rats, the NOAEL of 140 ppm, equal to 9.3 mg/kg bw per day, was based on reduced body-weight gain and food consumption at doses 960 ppm, equal to 63 mg/kg bw per day. Behavioural effects were observed only in the “functional observational battery” in males at 3000 ppm, equal to 200 mg/kg bw per day.

Neurotoxicity

	Clinical signs and neurobehavioural effects ascribed to acute cholinergic toxicity; short-term effects related to general toxicity
NOAEL (acute neurotoxicity)	42 mg/kg bw
NOAEL (short-term study of neurotoxicity)	140 ppm (9.3 mg/kg bw per day)

86. INDOXACARB

Source: INDOXACARB 31 –3 JMPR 2005

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

Neurotoxicity/delayed neurotoxicity

	Evidence of neurotoxicity at high doses (100 mg/kg bw in females and 200 mg/kg bw in males)
Lowest relevant NOAEL	12.5 mg/kg bw (for reduced body-weight gain and food consumption)

ARfD 0.1 mg/kg bw Rat, acute neurotoxicity 100

In a study of **acute neurotoxicity** in rats, reduced body-weight gain and food consumption **occurred at doses** of 50 mg/kg bw and above in females and 200 mg/kg bw in males. The NOAEL was 12.5 mg/kg bw. In females, **evidence of neurotoxicity**, such as slightly reduced motor activity, **was observed at 100 mg/kg bw**. In males, a reduced forelimb grip strength and decreased foot splay was observed at 200 mg/kg bw.

87. IPRODIONE

FAO Plant Production and Protection Paper, 133, 1996 - Pesticide residues in food - 1995. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment

Source: JMPR REPORT 1995

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

Iprodione, a dicarboximide fungicide, was previously evaluated toxicologically by the JMPR in 1977 133 iprodione and 1992. An ADI of 0-0.2 mg/kg bw was allocated in 1992. Since that time, long-term carcinogenicity studies in rats and mice that included higher doses and supplemental studies of the possible mechanism of tumorigenicity have become available and were evaluated by the present Meeting.

An ADI of 0-0.06 mg/kg bw was established on the basis of an NOAEL of 6 mg/kg bw per day in the most recent two-year study of carcinogenicity in rats and a safety factor of 100.

88. KRESOXIM-METHYL

FAO Plant Production and Protection Paper, 148, 1999 - Pesticide residues in food - 1998. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group.

Source: JMPR REPORT 1998

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

Neurotoxicity / Delayed neurotoxicity	No data

89. ISOPROTHIOLANE

Source: JMPR

Kind of Neurotoxicity: NO DATA

90. LUFENURON

Source: LUFENURON 453–500 JMPR 2015

Kind of Neurotoxicity: SUBCHRONIC NEUROTOXICITY

Neurotoxicity:

Acute neurotoxicity NOAEL	No evidence of acute neurotoxicity
Subchronic neurotoxicity NOAEL	**5.43 mg/kg bw per day (4 months; rat)**
Developmental neurotoxicity NOAEL	No data

91. MANDIPROPAMID

Source: MANDIPROPAMID 173–196 JMPR 2008

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity:

Acute neurotoxicity and studies of short-term neurotoxicity	No indications of neurotoxicity in studies of acute toxicity or repeat-dose studies

92. MANEB (dithiocarbamates)

FAO Plant Production and Protection Paper, 122, 1993 - Pesticide residues in food - 1993. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues

Source: JMPR REPORT 1993

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

Maneb or the sum of any combination of maneb, mancozeb, and zineb, of which not more than 0.002 mg/kg bw may be present as ethylenethiourea (ETU).

GROUP ADI WITH MANCOZEB, METIRAM & ZINEB → 0.03

93. METAFLUMIZONE

Source: METAFLUMIZONE 357–418 JMPR 2009

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity:

Acute neurotoxicity	No evidence of neurotoxicity; NOAEL: 2000 mg/kg bw (highest dose tested)
Subchronic neurotoxicity	No evidence of neurotoxicity; NOAEL: 300/150 mg/kg bw per day (highest dose tested; 90-day study in rats)

94. METALAXYL – METALAXYL-M

Source: METALAXYL AND METALAXYL-M 165-221 JMPR 2002

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity	No concerns arising from available information

95. METHAMIDOPHOS

Source: METHAMIDOPHOS 223-253 JMPR 2002

Kind of Neurotoxicity: ACUTE – SHORT – DELAYED NEUROTOXICITY

Acute Neurotoxicity NOAEL: 0.3 mg/kg bw for inhibition of cholinesterase activity (rats)

ARfD 0.01 mg/kg bw

90-day	NOAEL: 1ppm (equal to 0.067 mg/kg bw for inhibition of cholinesterase activity, rats)
Delayed Polyneuropathy	Signs of delayed polyneuropathy observed at doses above the LD_{50}

96. METHIDATHION

FAO Plant Production and Protection Paper, 145, 1998 - Pesticide residues in food - 1997. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group.

Source: JMPR REPORT 1997

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

In another study of acute neurotoxicity in rats, changes in clinical signs, the results of a battery of functional observational tests, and maze activity were observed at the time of peak effect (about 2 h after treatment) at 8 mg/kg bw and above in males and at 4 mg/kg bw and above in females. Inhibition of acetylcholinesterase activity in various regions of the brain was found at doses of 4 mg/kg bw and above. Reduced acetylcholinesterase activity in the cortex and hyppocampus of a male treated with 1 mg/kg bw was not considered to be relevant. The overall NOAEL in this study was 1 mg/kg bw.

97. METHIOCARB

FAO Plant Production and Protection Paper, 148, 1999 - Pesticide residues in food - 1998. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group.

Source: JMPR REPORT 1998

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/Delayed neurotoxicity Does not cause delayed polyneuropathy

In an early study of neurotoxicity in hens, methiocarb did not cause delayed polyneuropathy of the organophosphorus type. Atropine has consistently been shown to be an effective antidote for methiocarb, while the effects of pyridinium oximes were somewhat inconsistent.

98. METHOMYL

FAO Plant Production and Protection Paper, 167, 2001 - Pesticide residues in food - 2001. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group.

Source: JMPR REPORT 2001

Kind of Neurotoxicity: ACUTE – SHORT TERM NEUROTOXICITY

Rat:

Acute neurotoxicity after administration by gavage	Inhibition of erythrocyte and brain cholinesterase NOAEL 0.25 mg/kg bw LOAEL 0.5 mg/kg bw
Acute neurotoxicity after administration in the diet	Reduced response to tail pinch NOAEL 1.0 mg/kg bw LOAEL 1.9 mg/kg bw
13-week study of **neurotoxicity** after administration in the diet	Clinical signs and brain cholinesterase inhibition NOAEL 150 ppm (equal to 9.4 mg/kg bw per day) LOAEL 1500 ppm (equal to 95 mg/kg bw per day)

99. METHOXYCHLOR

Source: JMPR

Kind of Neurotoxicity: NO DATA

ONLY ADI

100. METHOXYFENOZIDE

Source: METHOXYFENOZIDE 161–202 JMPR 2003

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity:

Acute neurotoxicity	NOAEL: >2000 mg/kg bw; no neuropathy (rat)
90-day study of neurotoxicity	NOAEL: 1318 mg/kgbw per day (highest dose tested); no neuropathy (rat)

101. MIREX

Source: JMPR

Kind of Neurotoxicity: NO DATA

102. MONOCROTOPHOS

FAO Plant Production and Protection Paper, 122, 1993 - Pesticide residues in food - 1993. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues.

Source: JMPR REPORT 1993

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

103. MYCLOBUTANIL

Source: MYCLOBUTANIL 357–405 JMPR 2014

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

Neurotoxicity

Acute neurotoxicity NOAEL	No data
Subchronic neurotoxicity NOAEL	No data
Developmental neurotoxicity NOAEL	No data

104. OXADIXYL

Source: JMPR

Kind of Neurotoxicity: NO DATA

105. OXAMYL

Source: OXAMYL 255-282 JMPR 2002

Kind of Neurotoxicity: ACUTE-SHORT TERM NEUROTOXICITY

Neurotoxicity	Inhibition of cholinesterase activity in brain, plasma and erythrocytes and clinical and behavioural effects associated with cholinesterase inhibition
Lowest relevant oral	
NOAEL	0.1 mg/kg bw, rats
Delayed neurotoxicity	No concern

Acute neurotoxicity /Neurotoxicity effect	NOAEL 0.1mg/kg bw LOAEL 0.75 mg/kg bw
90- day neurotoxicity /Neurotoxicity effect	NOAEL 30 ppm, equal to 1.7 mg/kg bw per day LOAEL250 ppm, equal to 15 mg/kg bw per day

106. PENCONAZOLE

Source: PENCONAZOLE 501–558 JMPR 2015

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

Neurotoxicity

Acute neurotoxicity NOAEL	No data
Subchronic neurotoxicity NOAEL	No data
Developmental neurotoxicity NOAEL	No data

107. PENCYCURON

Source: JMPR

Kind of Neurotoxicity: NO DATA

108. PENDIMETHALIN

Source: JMPR

Kind of Neurotoxicity: NO DATA

ONLY ADI

109. PHOSALONE

FAO Plant Production and Protection Paper, 167, 2001 - Pesticide residues in food - 2001. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group.

Source: JMPR REPORT 2001

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

There is no evidence that phosalone has the potential to cause delayed neuropathy.

110. PHOSMET

Source: PHOSMET 267–273 JMPR 2003

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

In study of acute neurotoxicity in rats given phosmet by gavage, erythrocyte acetylcholinesterase activity was inhibited by >70% at 22.5mg/kgbw and by about 10% at 4.5mg/kgbw. Brain acetylcholinesterase activity was inhibited by >60% at 22.5mg/kgbw (Cappon, 1998). These results suggest that rabbits given phosmet at a dose of 15mg/kgbw (as in the study of developmental toxicity by Moxon, 1991) would show significant inhibition of acetylcholinesterase activity.

The 1998 JMPR concluded that: ". . . there was no evidence that phosmet could produce clinical signs of delayed polyneuropathy or significantly inhibit neuropathy target esterase" (Annex 1, reference 85).

The Meeting established an acute RfD of 0.2mg/kgbw based on the NOAEL of 2mg/kgbw (the highest dose tested) for inhibition of erythrocyte cholinesterase in men and women, and a safety factor of 10.

111. PARATHION-METHYL

FAO Plant Production and Protection Paper, 133, 1996 - Pesticide residues in food - 1995. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment.

Source: JMPR REPORT 1995

Kind of Neurotoxicity: CHRONIC NEUROTOXICITY

In a **one-year study** in rats to determine the ocular and neurotoxic effects of parathion-methyl, dietary levels of 0, 0.5, 2.5, 12 or 50 ppm were administered. Ocular toxicity was not observed. **Degenerative changes of the sciatic nerve and its extensions consistent with demyelination were observed at the two highest doses.**

In **another two-year study in rats**, parathion-methyl did not induce carcinogenic effects. The **NOAEL was 5 ppm** (equivalent to 0.25 mg/kg bw per day) on the basis of the observation of tremors, anogenital staining, reduced body weight, retinal

degeneration, **sciatic nerve degeneration, decreased packed cell volume and haemoglobin and erythrocyte counts, and decreased brain cholinesterase activity in males and females at 50 ppm (equivalent to 2.5 mg/kg bw per day).**

An **ADI** of **0-0.003** mg/kg bw was established on the basis of the NOAEL of 5 ppm, equivalent to 0.25 mg/kg bw per day, in **the two-year study** in rats for retinal degeneration, sciatic nerve demyelination, **reduced body weight, anaemia, and decreased brain acetylcholinesterase activities**. A safety factor of 100 was used. Since the toxicological end-points seen in animals were other than acetylcholinesterase inhibition, a safety factor of 10 could not be applied to the NOAEL in humans.

An **acute reference dose** of 0.03 mg/kg bw was derived by applying the usual 10-fold safety factor from an NOAEL of 19 mg/kg bw (highest oral dose), corresponding to about 0.3 mg/kg bw per day, in humans. **This was based on the absence of inhibition of erythrocyte acetylcholinesterase.**

112. PENTACHLOROBENZENE

Source: JMPR

Kind of Neurotoxicity: NO DATA

113. PERMETHRIN

FAO Plant Production and Protection Paper, 153, 1999 - Pesticide residues in food - 1999. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group.

Source: JMPR REPORT 1999

Kind of Neurotoxicity: ACUTE – SHORT TERM NEUROTOXICITY

Neurotoxicity/Delayed neurotoxicity	NOAEL, 150 mg/kg bw, single dose, rats; NOAEL ,15.5 mg/kg bw per day in a 90-day study, rats No acute delayed effect in hens (9050 mg/kg bw)

The results of acute and 90-day studies of neurotoxicity in rats and of an acute delayed neurotoxicity study in hens showed that technical-grade permethrin does not

induce neuropathological changes. The NOAEL for neurotoxicity in a study in rats given a **single dose was 150 mg/kg bw, on the basis of clinical signs of neurotoxicity** and significant changes in measurements in a functional observational battery of tests at 300 mg/kg bw. The **NOAEL for neurotoxicity in a 13-week study** in rats was 15 mg/kg bw per day, on the **basis of clinical signs of neurotoxicity** and significant changes in measurements in the functional observational battery of **tests at 90 mg/kg bw per day.**

114. PHENYLPHENOL

Source: JMPR

Kind of Neurotoxicity: NO DATA

115. 2-PHENYLPHENOL

FAO Plant Production and Protection Paper, 153, 1999 - Pesticide residues in food - 1999. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group

Source: JMPR REPORT 1999

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/Delayed neurotoxicity

No evidence of developmental neurobehavioral toxicity in rats. No evidence of neurotoxicity or neuropathology in medium- and long-term studies, mice, rats, dogs, or in developmental toxicity studies, mice, rats and rabbits.

116. PROMETRYN

Source: JMPR

Kind of Neurotoxicity: NO DATA

117. PIPERONYL BUTOXIDE

Source: JMPR REPORTS 1992 & 1995

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

118. PIRIMICARB

Source: PIRIMICARB 207–279 JMPR 2004

Kind of Neurotoxicity: ACUTE – SHORT TERM NEUROTOXICITY

Neurotoxicity/delayed neurotoxicity

Target/critical effect Nervous system/cholinergic signs

Lowest relevant NOAEL 10 mg/kg bw

90-day neurotoxicity

Target/critical effect Nervous system/cholinergic signs

Lowest relevant NOAEL 77mg/kg bw per day

ARfD 0.1mg/kg bw Rat; mortality and clinical signs of neurotoxicity in a study of acute neurotoxicity 100

119. PIRIMIPHOS-METHYL

Source: PIRIMIPHOS-METHYL X-X JMPR 2006

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

Two single-dose studies of neurotoxicity in rats were available. In the first, after administration of a high dose (1000 mg/kg bw) of pirimiphos-methyl, maximum inhibition (61%) of brain acetylcholinesterase activity was found after 24 h. Partial recovery was apparent at 48–72 h. In the second single-dose study of neurotoxicity, rats treated with pirimiphos-methyl at 150 or 1500 mg/kg bw showed dose-dependent reductions in erythrocyte and brain acetylcholinesterase activity 24 h after administration. In the animals at the highest dose, brain acetylcholinesterase activity had only partially recovered by day 15 after treatment. On the basis of the inhibition in brain cholinesterase activity at 24 h, the NOAEL was 15 mg/kg bw.

In one 28-day and one 56-day study in humans, pirimiphos-methyl was administered orally at a dose of 0.25 mg/kg bw per day. In neither study was inhibition of erythrocyte acetylcholinesterase activity nor any other toxicologically relevant effect observed.

Rat Acute neurotoxicity Neurotoxicity NOAEL 15 mg/kg bw

LOAEL 150 mg/kg bw

In establishing an ARfD, the Meeting concluded that it is appropriate to use data on inhibition of acetylcholinesterase activity in rats from a single-dose study of neurotoxicity in which a NOAEL of 15 mg/kg bw was identifi ed. Based on this NOAEL, the Meeting established an ARfD of 0.2 mg/kg bw, using a safety factor of 100.

120. PROCHLORAZ

Source: JMPR REPORT 2001

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity	No concern from other studies

121. PROCYMIDONE

Source: PROCYMIDONE 349–401 JMPR 2007

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity	No evidence in conventional studies

122. PROFENOFOS

Source: PROFENOFOS 403–443 JMPR 2007

Kind of Neurotoxicity: ACUTE – DNT NEUROTOXICITY

Neurotoxicity/delayed neurotoxicity

Acute neurotoxicity	Inhibition of brain acetylcholinesterase activity, NOAEL was 100 mg/kg bw per day (rats)
Developmental neurotoxicity	Inhibition of brain acetylcholinesterase activity, NOAEL was 5.1 mg/kg bw per day (rats)
Delayed neuropathy	No delayed neurotoxicity, NOAEL was 45.7 mg/kg bw (chickens)

ARfD 1 mg/kg bw Rat, **study of acute neurotoxicity** 100

In studies of acute neurotoxicity in rats, identified on the basis of clinical signs of neurotoxicity seen at >=200 mg/kg bw and inhibition of brain acetylcholinesterase activity at 400 mg/kg bw and using a safety factor of 100.

The Meeting established an ADI of 0–0.03 mg/kg bw per day based on an overall NOAEL of 2.9 mg/kg bw per day identified on the basis of inhibition of brain acetylcholinesterase activity in three short-term studies in dogs and using a safety factor of 100. This ADI was supported by the NOAEL of 5.1 mg/kg bw per day identified on inhibition of maternal and pup brain acetylcholinesterase activity in a study of developmental neurotoxicity in rats and a NOAEL of 4.5 mg/kg bw per day identified on the basis of inhibition of brain acetylcholinesterase activity in a 2-year study in mice.

123. PROPAMOCARB

Source: JMPR REPORT 2005

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

ARfD	2 mg/kg bw	Rat, acute neurotoxicity	100

Neurotoxicity/delayed neurotoxicity	Neurotoxicity Decreased activity 1 h after a single dose administered by gavage (rats) Vacuolization of the choroid plexus in the brain after repeated dosing (rats)
Lowest relevant oral NOAEL	200 mg/kg bw (single dose by gavage) 52 mg/kg bw per day (repeated dietary dosing)

124. PROPARGITE

FAO Plant Production and Protection Paper, 153, 1999 - Pesticide residues in food - 1999. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group

Source: JMPR REPORT 1999

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/Delayed neurotoxicity	No evidence of neurotoxicity

125. PROPICONAZOLE

Source: PROPICONAZOLE 281–323 JMPR 2004

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

Neurotoxicity/delayed neurotoxicity No specific studies; no findings in other studies

126. PROPOXUR

Source: JMPR

Kind of Neurotoxicity: NO DATA

ONLY ADI

127. PYMETROZINE

Source: PYMETROZINE X–X JMPR 2014

Kind of Neurotoxicity: ACUTE – SUBCHRONIC NEUROTOXICITY

Acute neurotoxicity NOAEL	< 125 mg/kg bw per day, lowest dose tested (rat)
Subchronic neurotoxicity NOAEL	68 mg/kg bw per day (rat)
Developmental neurotoxicity NOAEL	No data

The acute neurotoxicity of pymetrozine was investigated in rats at doses of 0, 125, 500 and 2000 mg/kg bw. Three males died at 2000 mg/kg bw. Dose-related reductions in locomotor activity were seen in all dose groups at 4–5 hours post-dosing, but not subsequently. There were no indications of neuropathy. No NOAEL was identified.

In a subchronic (90-day) neurotoxicity study in rats, dietary concentrations were 0, 500, 1000 and 3000 ppm (equal to 0, 35, 68 and 201 mg/kg bw per day for males and 0, 41, 81 and 204 mg/kg bw per day for females, respectively). The NOAEL for neurotoxicity and systemic toxicity was 1000 ppm (equal to 68 mg/kg bw per day), based on altered behaviours (continuous head movements and abnormal gait) and reduced body weights at 3000 ppm (equal to 201 mg/kg bw per day). There was no evidence of neuropathy.

128. PYRACLOSTROBIN

Source: PYRACLOSTROBIN 275–319 JMPR 2003

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Pyraclostrobin was not found to be neurotoxic.

129. PYRAZOPHOS

FAO Plant Production and Protection Paper, 116, 1993 - Pesticide residues in food - 1992. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues

Source: JMPR REPORT 1992

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Pyrazophos did not cause delayed neuropathy in hens.

In a 92/96 (female/male) week study in mice at dietary concentrations of 0, 1, 5 or 25 ppm, pyrazophos did not cause adverse effects up to the highest nominal concentration of 25 ppm, equal to 3.5 and 4.1 mg/kg bw/day in males and females, respectively. Inhibition of serum and erythrocyte cholinesterase activities but not of brain acetyl cholinesterase activity was observed at 5 ppm and above. The poor correspondence between actual and nominal concentrations of pyrazophos in diets hampered definitive evaluation of this study.

In a two-year study in rats at dietary levels of 0, 2, 80 or 320 ppm, the NOAEL was 2 ppm, equal to 0.1 mg/kg bw/day, based on a higher incidence of hemangiomas in mesenteric lymph nodes detected in males at the higher doses. Marginal brain acetyl cholinesterase inhibition was noted at 320 ppm only.

In a two-year study in rats at dietary concentrations of 0, 5, 8, 10 or 50 ppm the NOAEL was 50 ppm, equivalent to 2.5 mg/kg bw/day, based on the absence of adverse effects including brain acetyl cholinesterase inhibition at this dose level. No compound-related abnormalities were detected in mesenteric lymph nodes.

130. PYRETHRINS (PYRETHRIN I)

FAO Plant Production and Protection Paper, 116, 1993 – Pesticide residues in food – 1992. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues

Source: JMPR REPORT 1992

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

In a study of neurotoxicity in rats given single oral doses, acute neurological disorders (tremors, wetness of the urogenital area, salivation, perinasal encrustation,

exaggerated startle response, decreased grip strength, and hind-leg splay) and behavioural effects (increased motor activity and decreased rearing and ambulation) were noted, with a NOAEL of 20 mg/kg bw.

131. PYRIDABEN

Source: JMPR

Kind of Neurotoxicity: NO DATA

132. PYRIMETHANIL

Source: PYRIMETHANIL 445–486 JMPR 2007

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity

Acute neurotoxicity	No sign of specific neurotoxicity

133. PYRIPROXYFEN

FAO Plant Production and Protection Paper, 153, 1999 - Pesticide residues in food - 1999. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group

Source: JMPR REPORT 1999

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/Delayed neurotoxicity	No evidence of developmental neurobehavioural toxicity in rat. No evidence of neurotoxicty or neuropathology in medium- or long-term studies in mouse, rat, dog or during development in rat, rabbit.

134. QUINALPHOS

Source: JMPR

Kind of Neurotoxicity: NO DATA

135. SPINOZAD

FAO Plant Production and Protection Paper, 167, 2001 - Pesticide residues in food - 2001. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group

Source: JMPR REPORT 2001

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity was investigated in rats by giving them a single dose of up to 2000 mg/kg bw, doses up to 43 mg/kg bw per day for 3 months, or doses up to 49 mg/kg bw per day for 12 months. Comprehensive behavioural and histopathological investigations revealed no evidence of neurotoxicity.

Neurotoxicity/Delayed neurotoxicity

No evidence of neurotoxicity in a 12-month study in rats at doses up to 49 mg/kg bw per day

136. SPIRODICLOFEN

Source: SPIRODICLOFEN 419–496 JMPR 2009

Kind of Neurotoxicity: SUBCHRONIC NEUROTOXICITY

Neurotoxicity/delayed neurotoxicity

Acute neurotoxicity	No evidence of neurotoxicity; NOAEL: 1000 mg/kg bw per day
Subchronic neurotoxicity	**Decreased motor and locomotor activity** (females only); NOAEL: 87 mg/kg bw per day
Developmental neurotoxicity	No evidence of developmental neurotoxicity

Neurotoxicity was investigated in a study of acute neurotoxicity, a short-term study of toxicity and studies of developmental neurotoxicity in rats. There was no evidence of neurotoxicity in the study of acute neurotoxicity, and the only **evidence of neurotoxicity** in the **short-term study** was decreased motor and locomotor activity in females at 12 500 ppm, equal to 1310 mg/kg bw per day (the limit dose), during 1 week of treatment.

Two studies of developmental neurotoxicity were conducted. Overall, the Meeting considered that these studies did not indicate any treatment-related fi ndings on neurotoxicity parameters in offspring.

137. SPIROMESIFEN

Source: JMPR

Kind of Neurotoxicity: NO DATA

138. SPIROXAMINE

Source: JMPR

Kind of Neurotoxicity: NO DATA

139. SULFON

Source: JMPR

Kind of Neurotoxicity: NO DATA

140. SULFUR

Source: JMPR

Kind of Neurotoxicity: NO DATA

141. TEBUCONAZOLE

Source: TEBUCONAZOLE 503–564 JMPR 2010

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

Neurotoxicity/delayed neurotoxicity

Acute neurotoxicity	Increased motor activity in rats
Subchronic neurotoxicity	No neurotoxicity in rats
Developmental neurotoxicity	No neurodevelopmental toxicity in rats

In a study of **acute neurotoxicity** in rats with tebuconazole, the NOAEL was 50 mg/kg bw based on **increased motor activity in male and female rats and decreased footsplay in female** rats at 100 mg/kg bw. In a 90-day study of neurotoxicity in rats, no systemic or neurotoxic effects were seen at doses up to 1600 ppm (equal to 107 mg/kg bw per day), the highest dose tested. In a developmental neurotoxicity study in rats with dietary administration, the maternal NOAEL was 300 ppm (equal to 22 mg/kg bw per day), based on decreased body weights, body weight

gains and feed consumption, prolonged gestation with mortality and an increased number of dead fetuses at 1000 ppm (equal to 65 mg/kg bw per day). The offspring toxicity NOAEL was 300 ppm (equal to 22 mg/kg bw per day), based on decreased pup viability, decreases in body weights and absolute brain weights, brain measurements and evidence of developmental delays seen at 1000 ppm (equal to 65 mg/kg bw per day), the highest dose tested. Tebuconazole did not produce neurobehavioural or neuropathological changes.

142. TEBUFENPYRAD

Source: JMPR

Kind of Neurotoxicity: NO DATA

143. TETRACONAZOLE

Source: JMPR

Kind of Neurotoxicity: NO DATA

144. TETRADIFON

Source: JMPR

Kind of Neurotoxicity: NO DATA

145. THIABENDAZOLE

Source: THIABENDAZOLE X-X JMPR 2006

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

In order to better understand the nature and duration of the reversible neuroactive effects observed in the main single-dose study of toxicity (Noakes, 2004b), and also to establish clear NOAELs for all observation periods, an additional study was conducted.

These reversible neuroactive effects were similar in severity and duration to those observed at 100 mg/kg in the preceding study in rats treated by gavage (Noakes, 2004b). There were no toxicologically significant effects on body weight. Slightly low food consumption was seen for females treated with thiabendazole at 100 mg/kg bw on day 1 only.

Single-dose studies of toxicity: Three single-dose studies of toxicity in rats were provided for assessment by the present Meeting. As the neuroactive effects observed at 100 mg/kg bw were marginal, the NOAEL was 100 mg/kg bw. In the dietary study, no treatment-related effects on clinical signs, FOB assessment, motor activity or body weight were observed at up to 600 ppm (equal to 46 mg/kg bw), the highest dose tested.

146. THIACLOPRID

Source: THIACLOPRID X-X JMPR 2006

Kind of Neurotoxicity: ACUTE NEUROTOXICITY

Neurotoxicity

Acute neurotoxicity	**Clinical signs, effects in FOB observations, decreased motor and locomotor activity**; NOAEL: 3.1 mg/kg bw
Subchronic neurotoxicity	No evidence of neurotoxicity; NOAEL: 101 mg/kg bw per day at highest dose tested
Developmental neurotoxicity	No evidence of developmental neurotoxicity; decreased body weight and delayed sexual maturation at maternally toxic doses; NOAEL: 4.4 mg/kg bw per day

147. THIAMETHOXAM

Source: THIAMETHOXAM 565–676 JMPR 2010

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity/delayed neurotoxicity	**No signs of neurotoxicity**

148. THIAMETHOXAM (+CLOTHIANIDIN)

Source: JMPR

Kind of Neurotoxicity: NO DATA

149. THIOPHANATE-METHYL

Source: THIOPHANATE-METHYL X-X JMPR 2006

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

In a study of acute neurotoxicity in rats, the NOAEL for general toxicity was 125 mg/kg bw on the basis of transient reductions in body-weight gains (including body-weight losses) and feed consumption at 500 mg/kg bw and above. The NOAEL for neurotoxicity was 2000 mg/kg bw, the highest dose tested.
In a short-term study of neurotoxicity in rats, the NOAEL for general toxicity was 500 ppm (equal to 30.3 and 34.9 mg/kg bw per day in males and females, respectively) on the basis of decreased body weights and feed consumption in females and increased liver and thyroid weights in both sexes at 2500 ppm. No neurohistological changes were seen at 2500 ppm. The NOAEL for neurotoxicity was 2500 ppm (equal to 149.6 and 166.3 mg/kg bw per day in males and females, respectively), the highest dose tested.

The Meeting concluded that it was not necessary to establish an ARfD for thiophanate-methyl in view of its low acute toxicity, the absence of relevant developmental toxicity that could be a consequence of acute exposure, the **absence of relevant findings in a study of acute neurotoxicity**, and the absence of any other toxicological effect that would be likely to be elicited by a single dose.

150. TOLCLOFOS-METHYL

FAO Plant Production and Protection Paper, 127, 1995 - Pesticide residues in food - 1994. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and a WHO Expert Group on Pesticide Residues.

Source: JMPR REPORT 1994

Kind of Neurotoxicity: SUBCHRONIC NEUROTOXICITY

Tolclofos-methyl did not cause delayed neuropathy in chickens.

In a nine-month toxicity study in which mice were fed tolclofos-methyl in the diet at 0, 10, 30, 100 or 3000 ppm the NOAEL was 100 ppm, equal to 12 mg/kg bw per day, on the basis of inhibition of brain cholinesterase and effects on body weight at 3000 ppm.

In a 32-34-day toxicity study in which rats were fed diets containing 0, 200, 1000, 5000 or 20,000 ppm the NOAEL was 1000 ppm, equal to 79 mg/kg bw per day, on the basis of inhibition of brain cholinesterase and increased relative kidney weight at 5000 ppm. In a 13-week toxicity study in which rats were fed diets containing 0, 100, 1000 or 10,000 ppm the NOAEL was again 1000 ppm, equal to 66 mg/kg bw per day,

on the basis of effects on body, liver and kidney weights at 10,000 ppm. In a 28-week toxicity study in which rats were fed dietary levels of 0, 300, 1000, 3000 or 10,000 ppm the NOAEL was also 1000 ppm, equal to 65 mg/kg bw per day, on the basis of histopathological liver changes in females at 3000 ppm.

151. TRIADIMENOL AND TRIADIMEFON

Source: TRIADIMENOL AND TRIADIMEFON 325–386 JMPR 2004

Kind of Neurotoxicity: ACUTE-SUBCHRONIC NEUROTOXICITY

TRIADIMENOL:

Neurotoxicity/delayed neurotoxicity

Critical effects at LOAEL	See triadimefon
Lowest NOAEL	See triadimefon

TRIADIMEFON:

Neurotoxicity/delayed neurotoxicity

Critical effects	Increased activity in study of acute neurotoxicity after gavage administration (rat)
Lowest NOAEL	2 mg/kg bw
Critical effects	Increased activity in short-term feeding study (rat)
Lowest NOAEL	3.4 mg/kg bw

152. TRIAZOPHOS

Source: TRIADIMENOL AND TRIADIMEFON 325–386 JMPR 2004

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity

Delayed neuropathy	No concern for delayed polyneuropathy at doses relevant to human dietary intake

153. TRICHLORPHON

Source: JMPR

Kind of Neurotoxicity: NO DATA

ONLY ADI

154. TRICYCLAZOLE

Source: JMPR

Kind of Neurotoxicity: NO DATA

155. TRIFLOXYSTROBIN

Source: TRIFLOXYSTROBIN 387–450 JMPR 2004

Kind of Neurotoxicity: NO NEUROTOXICITY EVIDENCE

Neurotoxicity **No evidence of acute neurotoxicity** in rats

156. TRIFLURALIN

Source: JMPR

Kind of Neurotoxicity: NO DATA

157. VINCLOZOLIN

FAO Plant Production and Protection Paper, 133, 1996 - Pesticide residues in food - 1995. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO Toxicological and Environmental Core Assessment

Source: JMPR REPORT 1995

Kind of Neurotoxicity: NO NEUROTOXICITY DATA

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