

EU approval of pesticides and biocides regarding the identity, the physicochemical properties and methods of analysis. Use of monitoring data in the regulatory procedure.

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Abstract Pesticides and biocides consist a powerful tool in the agriculture and sanitary field, respectively, in order to satisfy the worldwide need for food and to protect human and animal health from unwanted pests. However, the indiscriminate misuse of these chemicals endangers environmental and human safety and for this reason they can be considered as emerging pollutants. Authorities worldwide establish regulations and guidelines regarding the authorization, use, monitoring and market control of pesticides in order to protect the environment and human safety. In this paper the data requirements for the approval of active substances, plant protection products and biocidal products as regards the identity the physicochemical properties and methods of analysis are described. The use of monitoring data in the regulatory procedure for the establishment of safe limits is also presented.

Keywords: Regulatory acceptable concentrations, plant protection product, biocidal product, drinking water, authorization

1. Introduction

Pesticides are defined by FAO (Food and Agricultural Organization) as substances or mixtures of substances intended for controlling, preventing, destroying, repelling or attracting any biological organism deemed to be a pest. The term pest includes insects, mice and other animals, weeds and fungi among others. In the European Union, pesticides are authorized according to Regulation EC No 1107/2009, concerning the placing of plant protection products on the market. According to this regulation, substances should only be included in plant protection products if they present a clear benefit for plant production and if harmful effect on human or animal health or any unacceptable effects on the environment are not expected.

Pesticides can be classified in a number of ways. In principal, they can be divided to plant protection products and to biocidal products. The first are used both in agriculture to protect crops and in forestry. In contrast, the

field of application of biocidal products involve human and veterinary hygiene, food preservatives and antifouling products among others, but not agriculture and related areas. Both of these main categories can be further classified according to the target organism, the chemical structure and the synthetic or natural origin of the active substance. Another classification concerns the formulation type of pesticides. Other types of classification involve the developmental stage affected, acute and chronic toxicity, general action on pests, biochemical or physiological activity, and application method.

Biocidal products are defined as active substances and preparations containing one or more active substances, put up in the form in which they are supplied to the user, intended to destroy, render harmless, prevent the action of, or otherwise exert a controlling effect on any harmful organism by chemical or biological means, according to the Directive 98/8/EC of the European Parliament and Council of the 16 February 1998, Biocidal products are authorized according to EU Regulation 528/2012. According to the same Regulation biocidal products are classified in twenty-two product types grouped in four main categories: Disinfectants, Preservatives, Pest control, and other biocidal products. Table 1 presents a detailed classification of the biocidal products.

Although the purpose of pesticide and biocide use is to provide an increased standard of living with sufficient food and protection from harmful organisms, the use of these products has also negative impacts on human health and the environment. Humans are exposed to pesticides by different routes of exposure such as inhalation, ingestion and dermal contact which may result in acute or chronic health problems. Additionally the environmental contamination from pesticides provokes non-target species poisoning and disturbance of the ecosystems. Due to the globalization of the pesticide market, the pesticide regulatory authorities legislate regulations for the authorization, proper use and disposal of pesticide products.

Table 1. Types of biocidal products

Disinfectants	Preservatives	Pest control	Others
<ul style="list-style-type: none"> • Human hygiene • Private area and public health area disinfectants • Veterinary hygiene • Food and feed area • Drinking water 	<ul style="list-style-type: none"> • Preservatives for products during storage • Film preservatives • Wood preservatives • Fiber, leather, rubber and polymerized materials preservatives • Construction material preservatives • Preservatives for liquid-cooling and processing systems • Slimicides • Working or cutting fluid preservatives 	<ul style="list-style-type: none"> • Rodenticides • Avicides • Molluscicides, Vermicides and products to control other invertebrates • Piscicides • Insecticides, Acaricides and products to control other arthropods • Repellents and attractants • Control of other vertebrates 	<ul style="list-style-type: none"> • Antifouling products • Embalming and taxidermist fluids

2. Data requirements

The data requirements for the approval of the actives substances and the plant protection products are defined in Commission Regulation (EU) No 283/2013 and 284/2013, respectively. The corresponding data requirements for biocidal active substances and products are defined by Regulation (EU) No 528/2012. The data requirements as regards the identity, the physicochemical properties and methods of analysis are similar for both pesticides and biocides.

2.1. Identity of active substance and the plant protection product

In general, the active substance should be identified by its ISO-name, CAS No, structural formula and molecular weight. The producer and the method of manufacture are declared and a specification on minimum purity of active substance and maximum content of relevant and significant impurities in the technical, supported by 5-batch analysis data for each manufacturing plant is proposed. Significant impurities are impurities present in quantities of 1 g/kg or more in the technical grade active substance. Relevant impurities are impurities that are particularly undesirable because of their toxicological, ecotoxicological or environmental properties.

If the active substance originates from a different/new producer, the equivalence with the EU approved manufacturing source must be established.

It is important to point out that there are often difficulties in the identification of active substances, especially of those that are characterized as UVCB (Unknown or Variable composition, Complex reaction products or Biological materials) or those that are of natural origin (ex:

botanical extracts). In those cases it is difficult to derive accurate specifications for the active substance.

The following information should be declared by the applicant of the plant protection product: The composition of the plant protection product (content of active substance and its variant, safeners, co-formulants, and maximum content of relevant impurities) and its producer. The technical grade active ingredient of the active substance should be originated from an EU approved manufacturing source. The product should be in compliance with with existing FAO limits for the active substance content in the formulation. Type and code of plant protection product should be declared according to 'Manual on development and use of FAO and WHO specifications for pesticides'.

2.2. Physicochemical properties of the active substance and the plant protection product

For the approval of the active substance its physicochemical properties such as appearance, melting/boiling point, vapour pressure, solubility in water/organic solvents, partition co-efficient, dissociation constant, spectra and surface tension are evaluated along with the safety properties (flash point, flammability, self-heating, explosive and oxidising properties) based on which classification and labelling according to Regulation 1272/2008 is proposed.

For the authorization of the plant protection products studies examining the following properties are evaluated: appearance, pH/acidity/alkalinity, viscosity, surface tension, density, storage stability at high/low/ambient temperature, physicochemical compatibility with other products and adherence/distribution to seeds. In addition, the technical properties of the plant protection product, depending on the type of the formulation, are evaluated according to CIPAC methods and compliance with the

relevant FAO/WHO specifications for pesticides should be confirmed. Finally the safety properties such as the flash point, flammability, self-heating, explosive and oxidising properties are examined and classification and labelling is proposed according to Regulation 1272/2008.

2.3. Analytical methods

The methods of analysis that are submitted for the evaluation of the active substance are divided in two categories: The methods used for the generation of pre-approval data and the method for post-approval control and monitoring purposes.

Methods used for the generation of pre-approval data:

The methods used for the generation of pre-approval data include the methods for the analysis of the active substance as manufactured and the methods for risk assessment. For the later, methods shall be submitted for the determination of non-isotope-labelled residues in all areas of the dossier, as set out in detail in the following points:

- (a) in soil, water, sediment, air and any additional matrices used in support of environmental fate studies;
- (b) in soil, water and any additional matrices used in support of efficacy studies;
- (c) in feed, body fluids and tissues, air and any additional matrices used in support of toxicology studies;
- (d) in body fluids, air and any additional matrices used in support of operator, worker, resident and bystander exposure studies;
- (e) in or on plants, plant products, processed food commodities, food of plant and animal origin, feed and any additional matrices used in support of residues studies;
- (f) in soil, water, sediment, feed and any additional matrices used in support of ecotoxicology studies;
- (g) in water, buffer solutions, organic solvents and any additional matrices used in the physical and chemical properties tests.

The specificity of the methods shall be determined and reported. Validated confirmatory methods shall be submitted if appropriate. The linearity, recovery and precision (repeatability) of methods shall be determined and reported. Data shall be generated at the LOQ and either the likely residue levels or ten times the LOQ. Where relevant, the LOQ shall be determined and reported for each analyte. The evaluation of these methods is based on the guidance document SANCO/3029/99 rev.4

Methods for post-approval control and monitoring purposes:

According to Regulation EC 1107/2009 Member States should carry out official controls in order to enforce compliance with the Regulation. For the control of pesticide products regarding the determination of the active ingredient and the relevant impurities competent authorities apply the official CIPAC methods (Collaborative International Pesticides Analytical Council) in case they are available. These methods are collaboratively tested by laboratories all over the world,

and after their evaluation and adoption, they are published in the CIPAC Handbooks. There are detailed specifications proposed by FAO (Food and Agriculture Organization) for agriculture pesticides and WHO (World Health Organization) for public health pesticides that these products must comply with, like the tolerance of the active ingredient content. In case that CIPAC methods are not available appropriate validated methods should be proposed by the applicant.

Enforcement methods for the determination of all components included in the respective monitoring residue definition in order to enable Member States to determine compliance with established maximum residue levels (MRLs), they shall cover residues in or on food and feed of plant and animal origin. Maximum Residue Levels (MRLs) are established by Regulation (EC) No 396/2005. According to EFSA, the MRLs are the upper legal levels of a concentration for pesticide residues in or on food or feed based on good agricultural practices. MRLs are derived after a comprehensive assessment of the properties of the active substance and the residue levels resulting from the good agricultural practices defined for the treated crops.

In addition methods the determination of all components included for monitoring purposes in the residue definitions for soil and water, and methods for the analysis in air of the active substance and relevant breakdown products formed during or after application should be submitted, unless it is shown that exposure of operators, workers, residents or bystanders is negligible. Finally, methods for the analysis in body fluids and tissues for active substances and relevant metabolites are required.

The specificity of the methods shall be determined and reported. It shall enable all components included in the monitoring residue definition to be determined. Validated confirmatory methods shall be submitted if appropriate. The linearity, recovery and precision (repeatability) of methods shall be determined and reported. Data shall be generated at the LOQ and either the likely residue levels or ten times the LOQ. The LOQ shall be determined and reported for each component included in the monitoring residue definition. For residues in or on food and feed of plant and animal origin and residues in drinking water, the reproducibility of the method shall be determined by means of an independent laboratory validation (ILV) and reported. The evaluation of the above methods is based on the guidance document SANCO/825/00 rev. 8.1

The applied monitoring methods need to be reliable, sensitive, specific and confirmatory, taking into consideration that the maximum permitted levels of pesticide residues in these complex matrices involve low concentrations (ppb). The most widely applied analytical techniques for enforcement purposes that fulfill these requirements are gas and liquid chromatography coupled to mass spectrometry (GC-MS(MS), LC-MS(MS) and LC-TOF-MS). Consequently, updated instrumentation, sensitive and robust analytical methods, qualified personnel, good laboratory practice and interlaboratory tests are very significant for the successful implementation

of the market control of pesticide products and the monitoring of pesticide residues

2.3. Use of monitoring data in setting regulatory limits

Monitoring data can be useful to the competent authorities in order to make regulatory decisions that will protect human and environmental health by reducing and eliminating the occurrence of pesticide contamination (Thodal C.E., Carpenter J. and Moses C.W. 2009). According to a pesticide monitoring study covering the main rivers and lakes of Northern Greece, the coupling of monitoring data to probabilistic human and ecotoxicological risk estimates could find use by Greek regulatory authorities, proposing effective pollution management schemes (N.Papadakis N. E *et al* 2015).

A comparison between monitoring data of pesticides in surface waters with regulatory acceptable concentrations determined in the authorization process and consideration for regulation has been presented by Knauer in Switzerland (Knauer K. 2016). The results indicated that a few pesticides in use might account for most of the concern for aquatic life. These pesticides with exceedances of the ecotoxicological thresholds were checked for a possible regulatory action. It was reported that implementing further risk mitigation measures might be advisable to reduce the exposure in aquatic systems.

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