GENERAL APPROACHES AND PROCEDURES FOR PESTICIDE LEGISLATION

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Abstract. The use of synthetic chemicals such as plant protection products (PPPs or 'pesticides'), especially in the last 60 to 70 years, greatly contributed to an impressive progress in the availability of food to an increasingly numerous mankind. However, the long-term consequences of the deliberate and unavoidable dispersion of these chemicals into the environment were long overlooked and generated health consequences to professional applicators, to bystander general population and to food consumers. An increased awareness of the potential threats of uncontrolled use of substances of poorly known toxicity led to a substantial change in the approach, gradually resulting into an improved legislation in Western Europe and in other developed countries, to the point that today licensed PPPs are among the substances of which the chemical and toxicological properties are best known, much before their introduction into the market and even better than requested for human pharmaceutical drugs. We will trace the pathway which leads to the birth of new PPPs and to their authorization according to the legislation of the European Union. In particular, while active substances are licensed for use in a 'positive list' at EU level, the different formulations suitable for use on different cultivations are authorized for the different geographical areas of EU with a 'mutual recognition' procedure between member States. Protection of agricultural workers, of consumers, of the environment are embedded into the authorization procedure by requesting that targeted studies run under normalized conditions are conducted prior to marketing. Several chemical and toxicological parameters

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which are pivotal to risk assessments towards humans, non-target plants and animals are measured and health-based safety levels are established for agricultural workers, for bystanders, for the general population, for the residual presence of the active substance and of its decomposition products in food and in natural drinkable water. For enhanced safety, authorization is released in 10-year periods, in order that unexpected harmful consequences for man and environment can be timely examined and, in case, tackled. The financial cost of this procedure is, of course, not without consequences. Since authorizations are issued in 10-year periods and are subject to voluntary rejuvenation by the licensees, there is a pressure to invest in newer, more profitable active substances rather than to keep into market older ones, which may be as efficient and cheaper, but for which the faintest evidence of health or environmental hazard may prematurely terminate corporate interest. The genesis of EU legislation will be discussed and examples will be brought to highlight key issues.

Keywords: Plant Protection Products, European Union, authorization, risk assessment

1. Characteristics of PPP

Plant protection products, or pesticides (insecticides, fungicides, herbicides) are chemical formulations which consist of one or more active ingredients (or active substances) and other ingredients. Their role is the protection of plants and crops in agriculture, horticulture, forestry and gardening. While Plant Protection Products (PPPs) differ in many ways from other chemical substances produced by humans, especially for manufacturing and industrial uses, they share several similarities with pharmaceuticals.

First, they are produced to control living species and therefore they are necessarily toxic; second, they are deliberately spread into the environment to reach their targets, therefore can be source of environmental pollution and human exposure (workers and consumers); third, they are produced to fight against pests, but the specificity of their toxicity for their targets is limited, therefore their use can endanger non target species, from useful insects such as bees to humans.

Moreover, it is accepted that without the use of pesticides a significant proportion of the agricultural production goes lost to spoilage in the fields and to rotting and deterioration throughout the production and distribution process, in particular in tropical countries, their use is unavoidable. In this perspective, the environmental and health risks related with their use need to be balanced by

the benefit they yield to agricultural production and, in the fight to disease-bearing parasites, to the benefit to public health.

The role of regulation processes is therefore to keep under constant control the consequences of the use of pesticides, with reference to a risk-benefit evaluation, and to prevent serious consequences to human health and to environment self-sustainability related to the use of these compounds.

Since the Council Directive of 1991, the European Union recognizes that plant production is very important for agriculture and plant protection products are one of the most important ways of protecting plants and plant products against harmful organisms including weeds, and of improving agricultural production (EC, 1991). Well alike pharmaceuticals, and different from most other commodities and consumer products, PPPs are long subject to pre-marketing authorization process which calls for knowledge of key information (physical, chemical, environmental and toxicological) characteristics to perform scenario-specific risk assessment. The introduction of the REACH (Regulation on Evaluation and Authorization of Chemicals) for nearly all industrial and consumer products takes most of its principles from the experience gained in the risk assessment of these high value-added products.

2. Regulation of Chemical Substances: a Glance to its History.

Although its principles were implicitly well-known since at least two centuries (the assessment of risk in long-distance trading of goods, which is the basis for setting insurance premium, is as old as Mesopotamic ages) Risk Assessment (RA) was formalized as a discipline in the USA towards the end of the 1970s. The necessity to frame the process arose as a consequence of two episodes which greatly stressed the public opinion and brought considerable debate into the scientific community: the consequences of the use of thalidomide as a drug and of vinyl chloride in the synthesis of PVC.

In the case of thalidomide, a sedative drug against morning sickness of pregnant women was deemed as fully safe after the reassuring outcome of what was reputed at the time to be sufficiently extensive safety tests on animal models and was marketed all over the world. It was prescribed to and taken by millions of pregnant women and, as a consequence, an epidemics of teratogenic effects soon developed, which stroke millions of children throughout the world and their families, before the use of the drug was banned (Brynner and Stephans, 2001). In the case of vinyl chloride, a chemical commodity was supposed to be reasonably safe in normal conditions of use and was widely used both as a monomer in the production of polymers for manufacturing uses, as a propellant for spraying in consumer products and it was evaluated even for the use as anesthetic gas. As manufacturing and use increased over a few decades,

evidence of its carcinogenic properties accumulated, finally leading to a ban in its use as a consumer product and to an increased level of care in its production and use as a chemical commodity (Markowitz and Rosner, 2005).

These two crucial episodes highlighted the need of performing a full toxicological assessment *before* any chemical substance could be authorized for industrial, pharmaceutical or other uses, and in particular if their use was, as in the case of pesticides, intrinsically dissipative.

Pesticides are one of the best examples to follow the thread of the development of risk assessment of chemical substances. Since its first introduction into the market, in 1939, DDT showed very good insecticidal properties and its production and use grew, widening its application from public health (control of human external parasites, such as lice and scabies), to environmental application in the eradication of Anopheles mosquito, the vector of malaria, from several endemic areas in temperate and tropical countries, to an efficient control of agricultural pests and even. Starting from the early sixties, with the publication of Rachel Carson's *Silent Spring*, concern on the environmental consequences of its widespread use reached the public opinion and the scientific community over the world started to investigate the bioaccumulation and bio-magnification properties of DDT through the food chain and its possible link to possible effects on human health. As awareness strengthened in the seventies, limitations and bans were raised in the most developed Countries, leading to a significant reduction of DDT production and use and finally to a generalized international ban (see Mrema et al., this volume). The same fate was followed by a few other pesticides, which are all characterized by common chemical characteristics leading to very long persistence in the environment, to transmission through the human food chain and by potential long-term toxicity.

Public perception of failures of pesticide regulation leading to strong public health concern and severe and persistent environment contamination has been a strong driving force towards improvement and harmonization of the requirements for authorization of plant protection products. The approach which is currently adopted for regulation of pesticides is "reactive/preventive", since it responds ('reactive') to damaging impacts for which there is convincing evidence of cause-effect relationship and takes regulatory action to ensure that similar impacts do not arise with new generation chemicals ('preventive'). It is also "risk-based" since it relies on cost-benefit analysis as a basis for scientifically rational decision making (Tait, 2001).

This approach is however not fully satisfactory, since existing knowledge of the complex interactions at the planetary scale is not sufficient to ensure that severe, irreversible consequences to the environment would not occur as the unexpected consequence of actions deemed devoid of risk according to existing

knowledge. To cope with such cases, more or less compelling versions of the (still undefined; COMEST, 2005) Precautionary Principle were appended. The 1992 Conference on the Environment and Development (UN, 1992), stated that: "*Where there are threats of serious and irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost effective measures to prevent environmental degradation*".

In the 1970s, to substitute for the fairly efficient but now unacceptably dangerous poly-chlorinated insecticides, new classes of products, devoid of accumulating potential and as quickly effective were developed, mainly the organo-phosphorous compounds (OPs), which derived from already well experimented although banned chemical warfare agents (the parent pesticide, parathion, was discovered at the German trust IG Farben in 1940). Due to their high acute toxicity and low specificity, at the beginning of their use several cases of acute and even fatal poisoning occurred to the point that workers often complained, requesting to authorize again the use of a compound perceived as safer during application, as is DDT.

The regulatory system for *new* chemical substances was therefore conceived to avoid to the widest possible extent the hazardous consequences of new products before they reach the market, rather than ex-post, on a case-by-case basis. As examples, when organophosphate pesticides replaced organochlorine pesticides, the higher acute toxicity of the former focused more attention on the safety of spray operators while, later, the introduction of pyrethroid insecticides, which have a much lower toxicity on humans and on mammalian animals, highlighted aquatic environment toxicity as the highest concern (Tait, 2001).

This approach grew in time to require the evaluation of toxic effects of new designer chemical entities to be used as PPPs towards several tens of different living organisms throughout the evolutionary cloud. As a consequence, knowledge of the biological effect of pesticides is even wider than that on pharmaceutical drugs, since it also covers toxicity towards non-target species and environmental fate. The necessity to obtain such data mandated the standardization of toxicological tests to be performed on sufficient numbers of animals to ensure statistically sound results, which in turn led to a widespread use of animal testing on bureaucratic, or 'defensive' rather than information-seeking basis. The heightened, albeit at the start and still minority, public perception of the existence of 'animal rights' (however this was declined in individual opinions) led to the necessity to arbitrate the opposite and little reconcilable positions by improving the quality of animal care and by better exploiting the advances in biochemical technologies (genetic engineering of animal strains, cell cultures, computational simulations) to achieve the '*3R*' aims of reduction (of the number of employed animals), of replacement (of

animal tests by alternative techniques) and of refinement (of animal tests to achieve crucial information unavailable by alternative techniques).

3. Development of New Pesticides.

That of pesticides-against-pests is, like that of antibiotics-against-microbes, a direct consequence of natural evolution on Earth. As pesticides are increasingly used to protect crops from their natural hosts, which compete with mankind for feeding on the same soil products or warm-blood animals from insects feeding on them, evolutionary pressure weeds out sensitive individuals and strains in favor of resistant ones. As an example, DDT-resistant mosquitoes were first detected in India in 1959, and they have increased so rapidly that when a local spray program is begun now, most mosquitoes become resistant in a matter of months rather than years. Mechanisms of acquired resistance include (Hemingway and Ranson, 2000; Rivero et al., 2010; Mitchell et al., 2012): (**a**) an improved metabolic detoxification through a point mutation of the gene coding for a P450 enzyme and by an increased activity of glutathione-S-transferase, (**b**) knockdown resistance (or kdr), caused by a reduction in the sensitivity of the insect nervous system to the insecticide, mostly through *point mutations* in sodium channel genes, which also allows resistance to pyrethroids (Matambo et al., 2007); (**c**) behavioural resistance or a shift in the insect's dwelling from the interior of treated houses to untreated outdoor areas (Bøgh et al., 1998; Wang et al., 2004). Analogous examples exist for the resistance of weeds to herbicides (Prather et al., 2000).

Developing new pesticides thus means finding chemical entities with multiple requirements:

- *activity* towards the targeted living species (weed, insect, warm-blood animal) through interference with an appropriately vulnerable biological pathway, which can develop at practically attainable doses;
- *resistance* to the environmental conditions of field application (sunlight, rain, high temperatures), in order that biologically active doses can reach the targeted living species;
- sufficient *selectivity* towards the targeted living species, *i.e.*, at environmental levels the product does not display toxicity towards non-target species, including humans, innocuous plants and insects, wildlife animals and fish, crops (including the plants to be treated), pollinating insects;
- farmer, consumer and environment *safety*, *i.e.*, can be employed in such conditions that agricultural workers are exposed at levels below which there

is concern for their health. the residues of the product do not enter into the human food chain and persist into food and water at levels above those of concern for health of the general population; the applied product does not persist in the environment after its efficacy is no longer required at levels of no concern for non-target species;

- *marketability*, *i.e.*, can be protected by patents, manufactured, authorized, delivered worldwide and applied safely in a range of climatic conditions, at a sustainable cost for the farmer.

While in 1972 'only' *approx.* ten thousand different chemical substances had to be screened for this characteristics in order to find one active substance deemed suitable for the market, in 2001, this number rose by 20 fold, meaning that 200,000 chemicals need to be screened to weed out one with all the required characteristics.

The scheme of Figure 1 outlines the general pathway followed for the selection of new candidate active substances and in their development as PPPs in industrial research. This pathway is closely similar to that followed to develop pharmaceutical drugs. Both activities are currently run in a global, highly competitive and highly regulated environment where fundamental research (or, better, fundamental research methodology) is aimed at investigating the molecular mechanisms of the physiology of target organisms, to seek unique metabolic pathways the disruption of which leads to death (Mode-of-Action; MoA). Chemical compounds able to interfere with target organism viability or with specific sensitive pathways are now selected with high-throughput screening platforms based on complex robotics, which enable them to test over 100,000 potential active molecules per year against whole living organisms or cultivated tissues. Potentially active molecules in agrochemical research are mainly of synthetic origin rather than natural substances as now increasingly common in pharmaceutical research, although there are several exceptions.

Useful compounds ('*hits*') are developed into families of structural analogues ('*leads*'), among which one or more with the most promising characteristics are selected for further study. Molecules with unfavorable characteristics (those less active, less stable, with unacceptably high acute toxicity) need to be sieved out as soon as possible, to ensure that intellectual and financial resources are focused on those most likely to end up into commercially viable products.

Thus it is only after several years of in-house research that a Company may be ready to apply for authorization of a new plant protection product. A substantial body of information, even greater than that required for a human drug, is supplied to the Authorizing bodies (in the EU, a Commission

headquartered in Brussels) in a standardized and legally binding form and subject to non-disclosure agreement ('Dossier'). This is a large technical-legal document, now distributed in digital form, in which the outcome of experimental tests requested by the authorization process and performed under relevant Good Practice codes are summarized in tables and refer to original data collected in files. Even after the authorization process has positively ended into an authorization or the product has been superseded or commercially abandoned the information is not disclosed for public use.

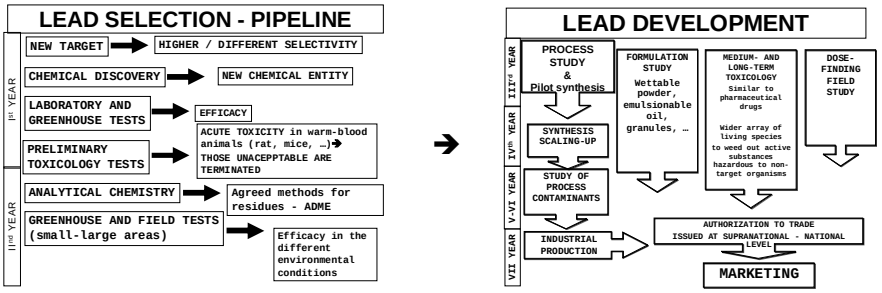

Figure 1. General pathway followed for the selection of new candidate active substances and in their development as PPPs in industrial research.

4. The Main Contents of Current Legislation on Pesticides in the European Union.

The regulation for the approval of active substances, of herbicide safeners and of synergists, enforces the precautionary principle as cited by Article 191.2 of the Consolidated Version of the Treaty on the Functioning of the European Union, which reads (EU, 2010):

"Union policy on the environment shall aim at a high level of protection taking into account the diversity of situations in the various regions of the Union. It shall be based on the precautionary principle and on the principles that preventive action should be taken, that environmental damage should as a priority be rectified at source and that the polluter should pay"

The main legislation to regulate the registration procedure of pesticides in the EU was the Council Directive 91/414/EEC of July 1991 concerning the placing of plant protection products on the market (EC, 1991). In 2009, in the light of experience gained from the application of the 1991 Directive and the "recent scientific and technical developments" that Directive was replaced by the Regulation No 1107/2009 of the European Parliament and of the Council

(EC, 2009), which is fully applicable as of 14 June 2011. This Directive has repealed, by way of simplification, the Council Directive 79/117/EEC (EC, 1978), which prohibits the placing on the market and use of plant protection products containing certain active substances.

According to current legislation, in the EU only Plant Protection Products with a current authorization ('*positive list*'; www) can be legally used, to the exception of any other. According to the principle of subsidiarity stated in Article 3b of the Treaty of the EU (EU, 2010), which reads:

*The Community shall act within the limits of the powers conferred upon it by this Treaty and of the objectives assigned to it therein. // In areas which do not fall within its exclusive competence, the Community shall take action, in accordance with the principle of subsidiarity, only if and in so far as the objectives of the proposed action cannot be sufficiently achieved by the Member States and can therefore, by reason of the scale or effects of the proposed action, be better achieved by the Community. // Any action by the Community shall not go beyond what is necessary to achieve the objectives of this Treaty. (*Art. 3b of the Consolidated Version of the Treaty on the Functioning of the European Union, Official Journal of the European Union*)*

The authorization of active substances is issued at EU level, while that of formulated products is issued by Member States' national authorities (usually the Ministry of Health) by adopting the procedure of Mutual Recognition.

The general principle of Mutual Recognition (EC, 2008) ensures the free movement of goods within the EU by avoiding the unnecessary duplication of controls. In the field of PPPs the standard procedure under the old legislation (EC, 1991) was that every product had to be authorized in each Member State separately, while the current one fully applies this fundamental EU principle (*see* 4.3).

4.1. AUTHORIZATION OF ACTIVE SUBSTANCES BY THE EUROPEAN UNION

In the European Union (EU), no plant protection product can be used unless it has first been scientifically established that: (***a***) they have no harmful effects on consumers, farmers, local residents and passers-by; (***b***) they do not cause unacceptable effects on the environment; (***c***) they are sufficiently effective against target pests. As a direct consequence, the components of plant protection products placed on the market must not adversely affect human or animal health or the environment. The current regulation also allows the States members of the European Union to apply the precautionary principle where

there is scientific uncertainty as to the risk with regard to human or animal health or the environment posed by the plant protection products.

The complex procedure leading to authorization of a new active substance as PPP is outlined in the scheme of Figure 2.

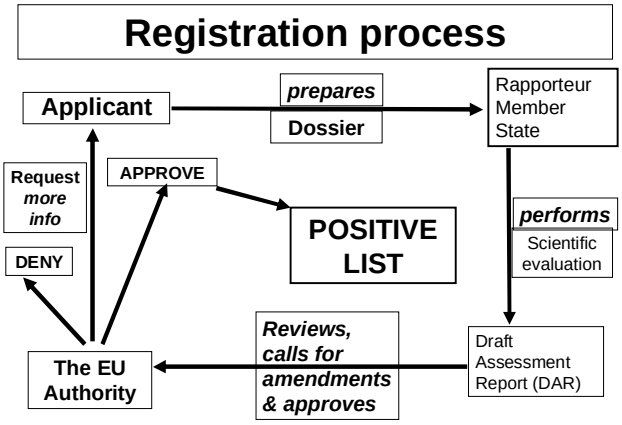

Figure 2. Procedure leading to authorization of a new active substance as PPP in the EU.

The Notifier or Applicant is (usually) the Company willing to have the active substance authorized for PPP use in the EU. The review of the information supplied in the Dossier is assigned to one Member State (Rapporteur), which is usually selected on the basis of the putative or requested use of the active substance and the expertise gained in the Country in reviewing products for that specific use (*e.g.*, grape in Southern European countries like France, Italy or Spain, potato in Central European countries like Germany or Ireland).

To apply for authorization of an active substance as PPP, the Applicant submits a dossier to the Member State which has been designated as the Rapporteur Member State (RMS). The dossier comprises all the study reports, data and information which are required by the Council Directive. The dossier is evaluated by the RMS and the results are summarized in a Draft Assessment Report (DAR). The DAR is then discussed by the Member States in a peer review process. The Member States, the EFSA and interested parties can comment on the DAR. Open matters to do with evaluation can be discussed in expert meetings (PRAPeR Expert Meetings) organized by the European Food Safety Agency (EFSA) for this purpose. Following the peer review, the EFSA sends a summary report, which includes its conclusions, to the European Commission. At the end of this process, the European Commission and the 27

Member States decide in a meeting with the Standing Committee on the Food Chain and Animal Health on the inclusion or non-inclusion of the active substance in Annex I of the Council Directive. The complete list of active substances submitted for EU approval is publicly accessible at the website of the Directorate General for Health and Consumers (SANCO, in the EU administrative jargon) (EC SANCO, 2012). For each active substance it is indicated the status and outcome of the authorization procedure. Sofar, nearly 500 active substances have been authorized.

This regulation, which is publicly available at the SANCO website (EC SANCO, 2012), applies to active substances that are intended for one or more of following uses:

- Protecting plants or plant products against all harmful organisms […];
- Influencing the life processes of plants (e.g. growth, other than as a nutrient);
- Preserving plant products (excluding products subject to EU provisions on preservatives);
- Destroying undesired plants or parts of plants;
- Checking or preventing undesired growth of plants.

The EU regulation applies also to other categories of substances which are usually mixed with the active substance in the production process, or prior to application:

- *Safeners*: substances or preparations which are added to a plant protection product to eliminate or reduce phototoxic effects of the plant protection product on certain plants;
- *Synergists*: substances or preparations that can give enhanced activity to the active substance(s) in a plant protection product;
- *Co-formulants*: substances or preparations which are used in a plant protection product, but are neither active substances nor safeners or synergists;
- *Adjuvants*: substances or preparations consisting of one or more co-formulants, to be mixed by the user with a plant protection product to enhance its effectiveness.

Therefore the European Union will authorize only active substances that are sufficiently effective under reasonable conditions of use; that do not have immediate or delayed harmful effect on human health, including that of vulnerable groups and on animal health, directly or through drinking water, food, feed or air, or consequences in the workplace or through other indirect effects; that do not have any unacceptable effects on plants or plant products;

that do not cause any unnecessary suffering and pain to vertebrates to be controlled; and finally that do not have any unacceptable effects on the environment.

4.2. AUTHORIZATION OF FORMULATIONS

In accordance to the Regulation 1107/2009 of the European Commission, Plant Protection Products (PPPs) can be authorized in a Member State and can be placed on the market only if it complies with the requirement that:

- All substances in it; active substances, safeners and synergists have been approved and, if any of them is produced by a different source, their properties cannot deviate significantly from those included in the Regulation approving the substance;
- It does not contain co-formulants which are included in Annex III of the Regulation 1107/2009 (List of co-formulants which are not accepted for inclusion in plant protection products)
- It is formulated so that user exposure or other risks are limited as much as possible without compromising the efficacy of the product;
- It complies with all the safety requirements for active substances and PPPs
- Its physical and chemical properties have been determined and deemed acceptable for the use and storage of the product;
- The nature and quantity of all components and its residues in the environment and in crops and food can be determined by appropriate methods.

4.3. NATIONAL AUTHORIZATION AND MUTUAL RECOGNITION

The regulation 1107/2009 has laid down harmonized rules for the approval of active substances and the placing on the market of plant protection products, including the rules on the mutual recognition of authorizations and on parallel trade. The goal is to increase free movement of such products and availability of these products in the Member states.

Under the new legislation, authorizations granted by one Member State should be accepted by other Member States where agricultural, plant health and environmental (including climatic) conditions are comparable. To facilitate such mutual recognition, the 27 Member States of the EU are assigned each to one of three zones with such comparable conditions. The zones of mutual recognition have been established as follows:

Zone A – North: Denmark, Estonia, Latvia, Lithuania, Finland, Sweden

Zone B – Centre: Belgium, Czech Republic, Germany, Ireland, Luxemburg, Hungary, Netherlands, Austria, Poland, Romania, Slovenia, Slovakia, United Kingdom

Zone C – South: Bulgaria, Greece, Spain, France, Italy, Cyprus, Malta, Portugal

The Member State may amend an authorization issued by another Member State, or refuse to authorize the plant protection product in their territory, where there are agricultural or environmental circumstances that require so, or where high level of protection of human and animal health, and the environment cannot be achieved.

4.4. RENEWAL AND REVIEW OF ACTIVE SUBSTANCES

To have the same level of protection for all Member States, the decision to approve a PPP, to deny or to withdraw the approval is taken at Community (EU) level and authorization is subject to renewal to account for new information that may be emerging from field use. This procedure is analogous to farmaco-vigilance carried by EMEA and by the National authorities for pharmaceutical drugs.

A comprehensive renewal procedure was first laid down in 1991 (EC, 1991), and in 1993 the European Commission launched the work program on the Community-wide review for all active substances used in the European Union. By that time, there were about 1,000 active substances and 10,000s of PPPs on the market. It was requested that each substance was re-evaluated to understand whether it could be still used safely with respect to human and environment health. To harmonize technical requirements and acceptance criteria, Directives have laid out comprehensive risk assessment and authorization procedures for active substances and products containing these substances. It is the responsibility of industry to provide the data showing that a substance can be used safely with respect to human health and the environment.

The decisions only started to be taken in 2001, since and in March 2009 last decisions were taken. From around 1000 active substances on the market in at least on Member State before 1993, only 250 (26%) passed the harmonized EU safety assessment. For the majority of eliminated substances (67%) dossiers were either not submitted, were incomplete or the industry spontaneously withdrew them from the market. This results show that most of the substances in use were fairly safe, as demonstrated by the fact that only about 70 substances failed the review and have been removed from the market, because

the evaluation carried out did not show safe use with respect to human health and the environment.

By the new Regulation, 1107/2009, first approval of a product can be for a period not exceeding 10 years, after which all active substances approved have to be reviewed to be renewed. Renewal cannot be granted for a period longer than 15 years, and for some active substances (those covered by Article 4(7): substances that do not comply to all of the conditions required by this Regulation, but are necessary to combat a pest in an urgent matter) authorization cannot be renewed for a period longer than 5 years.

This effort now provides assurance that the substances currently on the EU market are acceptable for human health and for the environment.

5. Setting the limits: AOEL, ADI, MRL, ARfD.

The use of PPPs necessarily entails the spread of active substances in the environment and the possibility that they contaminate workers, subjects of the general population and, through the general environment, also food and water sources. To protect humans from the possibly unavoidable contact with active substances in unnecessary and excessive amounts, limits need to be established during the regulatory process for the presence of PPP active substances at workplaces (mainly during pesticide application by farmers), as residues or contaminants in food and water and in the general environment. For each of these scenarios a different limit value has been developed.

5.1. ACCEPTABLE OPERATOR EXPOSURE LEVEL (AOEL).

Protection of agricultural workers' health when using Plant Protection Products features several fundamental differences and further difficulty with respect to the much simpler case of workers in the manufacturing industry, mainly outdoor rather than indoor work, continuously changing job, time and exposure patterns rather than Tayloristic schemes, prevalent skin than respiratory absorption route of employed chemicals. These differences point at whole-body dosimetry rather than environmental monitoring as the most convenient strategy to allow quantitative risk assessment. To this purpose, an Acceptable Operator Exposure Level (AOEL) has to be established. The AOEL is a systemic dose, normalized as milligrams of active pesticide substance per kilogram of body weight (mg * $kg_{bw}^{-1}]_{day}$) which an agricultural worker can absorb through professional exposure in any one working day so that there will be no negative health consequences. The AOEL is determined through an "health based approach", that is on the basis of animal toxicology experiments which take into consideration as endpoint the biological effect (relevant to the human) which

occurs at the lowest exposure level (the Lowes Observed (Adverse) Effect Level, LO(A)EL), then look for the (often extrapolated) exposure dose at which the effect is no longer observed in the most sensitive animal species (No Observed (Adverse) Effect Level, NO(A)EL). In turn, NO(A)EL values are extrapolated from animal studies (typically oral short-term toxicity studies; 90-day study, or occasionally 1-year dog study), performed in the pre-marketing development of a candidate active substance. (EC SANCO, 2006)

NO(A)EL is translated into AOEL by further dividing the 'safe' dose assessed in the suitable animal model by empirical reduction factors which account for the uncertainties existing in the extrapolation from animal toxicity data to safeguard levels for the human population. The current hazard assessment for toxic endpoints for which the existence of a no-effect threshold dose is assumed employs a (default) 100-fold uncertainty factor to extrapolate a 'safe' dose level for the general population based on animal toxicity data. The global 100-fold uncertainty factor is based on the assumption of a conservative 10-fold higher sensitivity of the human with respect to the most sensitive (or the default) animal species, and of a 10-fold difference of inter-individual variability in sensitivity between human subjects of the general population of different age, gender and general health status. In some cases, due to the low levels of intra-specie variability, the uncertainty factor applied for workers can be lower (2.5), but not (or seldom) lower values of the uncertainty factors can be applied when it is deemed that current unavoidable uncertainties recommend a more conservative approach to ensure that even the most sensitive human subject will go unharmed.

While it is commonplace that the use of agrochemicals by farmers is limited in time to the relatively short periods of application, whereas in the scenario of manufacturing industry exposure is considered to be continuous and appreciably constant throughout the working life of the person in the specific task, however it is also well-known that farmers' working life spans a much wider period of their lives, even from late childhood to late post-retirement age. As a consequence, adverse health effects occurring late in age as the consequence of chronic exposure should also be taken into account.

To improve risk assessment, any information on human exposure derived from scientifically sound and ethically sustainable observations and studies can be used to confirm the validity of regulatory limit values derived from animal studies, but at the moment it is not allowed to perform *ad-hoc* studies in human subjects to derive information for regulatory purposes and, in particular, no data collected on humans can be used to lower the safety margins resulting from tests or studies on animals (EC, 2009). Of course, during the re-authorization process, specific attention is addressed at the collection of epidemiological data coming from the use of the compound under evaluation.

5.1.1 The Use of the AOEL for Pre-marketing Risk Assessment

Pre-marketing risk assessment for occupational exposure to Plant Protection Products is a procedure aimed at demonstrating that the active substance, formulated as the commercial product(s) intended for marketing, is able to perform its task (*i.e.,* to suppress the target organism under field conditions) without causing inacceptable harm to the farm worker.

As in any risk assessment, the risk is calculated as the ratio of actual internal dose to the regulatory limit: acceptable risk is exceeded if the ratio is >1, *i.e.,* if the internal dose is higher than that allowed by the regulatory limit. This task is accomplished by (***a***) evaluating the dose of active substance which reaches the farmer during agricultural activities, (***b***) estimating the resulting internal dose and (***c***) comparing with the maximum dose allowed by the toxicity characteristics of the active substance and established as part of the authorization process.

As anticipated, all calculations use the main parameters which are obligatorily part of the information collected in the evaluation Dossier or in the studies supplied with the active substance for which the application has been submitted: the Acceptable Operator Exposure Level (the health-based AOEL), the skin absorption factor (which is either experimentally measured or defaulted to 100% if its direct determination is not feasible) and the concentration of active substance in the product.

The internal dose is calculated from the dose reaching the skin and the skin absorption coefficient, when this is available (otherwise defaulting to 100% skin absorption). In turn, the dose reaching the skin needs to be estimated from the amount of pesticide employed in a typical working day.

This quantity is often measured by performing studies in experimental farms, under standardized conditions, with workers doing spraying activities in different working scenarios, using different kinds of machineries, and different levels of protection. The resulting exposure is measured according to standardized methods, following the Guidelines of European Union (OCDE, 1997).

The measured levels of exposure for each working scenario and level of protection are then generalized as milligrams of active substance deposited on farmers' clothes per kilogram of active substance used (exposure), and the levels of protection afforded by different types of Personal Protection Devices are expressed as the percent fraction of exposure that reaches the worker's skin.

The various conditions which are able to influence the overall value of the fraction of used active substance which actually reaches the operator's skin are referred to as 'determinants of exposure'. The determinants covered by most models are collected in Table 1.

TABLE 1. Main determinants of exposure considered in the models for pre-marketing risk evaluation of Plant Protection Products in the EU.

Formulation type:	Liquid
	Wettable powder
	Wettable granules
Characteristics of the product:	Concentration of the active substance in the product
	Quantity of product used per hectare of field surface
Personal Protection Devices: worn in different phases	Respiratory protection (none, mask with filters)
	Hands protection (none, gloves)
	Head protection (none, hat)
	Body protection (none, coverall and footwear)
Container type (UK-POEM):	Capacity
	Closure (narrow or wide)
Work scenarios:	Target
	Tractor
	Hand-held
	Home-garden

Accepted models used to perform calculations in the regulatory setting are often available as computer spreadsheets (UK HSE, 2012) or as technical documents reporting the equations and from which appropriate calculation codes can be developed by interested professionals. Among those most commonly used are: the German Model (Lundehn et al, 1992), the EURO-POEM (van Hemmen, 2001), the UK-POEM (JMP, 1986). Publications in the refereed scientific literature often refer to these products as *de facto* standards for which informal agreement between practitioners exists, rather than formal independent validation.

One major criterion to consider a formulated product as safe for use is that the dose absorbed by the worker even in the absence of, or with the adoption of, minimal protection equipment is lower than the AOEL in all working scenarios which are relevant to product application.

5.2. ACCEPTABLE DAILY INTAKE (ADI).

This concept was first introduced in 1961 by the Council of Europe and later the Joint FAO/WHO Expert Committee on Food Additives (JECFA), a committee maintained the Food and Agriculture Organization FAO and the WHO World Health Organisation of the UNO. The ADI takes into account the unavoidable presence of residues of PPPs in food and in drinking water which

derive from the legitimate use of the formulated active substance, applied on crop cultures to protect them from pests, on crop products to prevent deterioration in their transport to food processing, to markets and to consumers, incorporated into meat and dairy from pasture and from silage, leaked into water reservoirs from use in the field.

An ADI value is established in the authorization process, based on the results of long-term studies on animals, by applying the same general criteria described above for the AOEL. Also the ADI is usually given in milligrams per kilogram of body weight ($mg * kg_{bw}^{-1}]_{day}$).

The ADI is considered a safe intake level for a healthy adult of normal weight when intake is appreciably constant in time. This may raise concern for substances with a tendency to show bio-accumulation in the organism or bio-magnification in the human food chain, as was the case with organo-chlorine pesticides, but currently the requirement for new active substances is that they are *per se* chemically labile in the environment, so that potential for build-up of levels of concern in the environment is now mostly negligible.

Increased safety factors for infants have been discussed, but are not needed, because elimination of chemicals is in fact often more rapid in children than in adults. The ADI does not take into account allergic reactions that are individual responses rather than dose-dependent phenomena.

5.3. MAXIMUM RESIDUE LEVELS (MRLS)

Conceptually closely related to the ADIs are the limit values referring to the maximum tolerable presence of residues in the several types of food which are produced and marketed downstream to the crops and in drinking water. Under the EU regulations, the Maximum Residue Levels (MRLs) are the upper legal levels of a concentration for pesticide residues in or on food or feed based on good agricultural practices and to ensure the lowest possible consumer exposure. The European Food Safety Authority (EFSA) is the administrative body of EU responsible for setting those limits. Regulation (EC) No 396/2005 (EC, 2005) establishes the MRLs of pesticides permitted in products of plant or animal origin intended for human or animal consumption.

MRLs are derived after a comprehensive assessment of the toxicological properties of the active substance (on the basis of which the ADI is established) and on the residue levels measured on or in crops treated according to the good agricultural practices defined for the product. Since consumer safety is the final aim for setting MRLs, values of the MRL are set at levels such that consumer intake of the active substance even in unbalanced diets based on food with the highest presence of residues does not exceed the ADI.

The maximum pesticide residue level in foodstuffs is 0.01 mg/kg for each active substance identified. This general limit is based on the expected sensitivity of available analytical methods and is applicable 'by default', *i.e.* in all cases where an MRL has not been specifically set for a product or product type. Some of the specific MRLs listed in Annex II are higher than the default limit, since there is evidence that the active substance is harmless to consumers' health.

In some cases, provisional MRLs may be set and should then be listed in Annex III. Provisional MRLs should in particular be set in the some cases, among which are the occurrence of exceptional circumstances (*e.g.*, emerging local phenomena of food contamination), and in the course of harmonization procedures.

The Member States have to carry out official controls on pesticide residues in order to enforce compliance with Maximum Residue Levels. The results of the controls have to be reported to the Commission, to the other Member States and to EFSA, which publishes an Annual Report on Pesticide Residues in the EU based on the monitoring information.

Products which do not comply with the fixed limits cannot be marketed to consumers and may not be diluted with products with a lower level of residues in order to lower the mean level to below the limit. except in the case of certain processed and/or composite products listed by the Commission (Annex VI). In exceptional cases, products which do not comply with the limits set in Annexes I and II may be authorized by a Member State if the products do not represent an unacceptable risk. It should in fact be considered that agricultural products are produced at a substantial environmental, labour and economic cost and that unnecessary discard and destruction or diversion from their food use is ethically unjustified unless higher-rank interests, such as that to health protection need to be enforced.

5.4. ACUTE REFERENCE DOSE (ARFD).

The need to consider acute effects of pesticide residue intake has been acknowledged for many years, and the concept of the Acute Reference Dose (ARfD) was developed by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 1994) in 1994. Since then, there has been a progressive increase in the establishment of ARfDs for particular pesticides to address potential exposure to residues in food and drinking water at relatively higher doses for short-term periods, due to accidental or incidental events. JMPR has continuously updated its procedure on the setting of ARfDs.

The ARfD is defined as "an estimate of the amount a substance in food or drinking water, normally expressed on a body weight basis, that can be ingested

in a period of 24 h or less without appreciable health risks to the consumer on the basis of all known facts at the time of the evaluation" (JMPR, 2002).

6. Risk Assessment in Post Marketing Phase

Even as an active substance is authorized in European Union, and products containing this active substance are authorized and marketed, there is still a need for risk assessment to communicate and to manage risk with regard to the different groups of stakeholders and to the general population as a whole (EC, 2009).

There may be concern within the general population for the alleged high level of residues in food staples, which may harm the long-term health of parents of unborn children, of babies, of otherwise weakened and of strongly health-seeking individuals. As a consequence, increased numbers of the population may move from the conventional food market to more demanding alternatives, such as less abundant products of biological agriculture, thus posing an often unnecessary pressure on their production and, due to their higher cost, to the economic system as a whole.

Leakage of herbicides and pesticides from treated soils and contamination of water tables, perturbation of insect populations of economic value, accidental if rare localized dispersion of bulk amounts of pesticides from production and packaging plants or during transportation and distribution are events through which the public opinion may feel higher-than-real threats and on regard of which fair and authoritative risk assessment, communication and management is both necessary and dutiful. Farmers may be concerned for their long-term health although occupational exposure to pesticides in the EU is traditionally considered to occur at low level and the consequent health risk is far from being a real source of concern. These different needs, although common in their necessity to be addressed by the public health authority, call for different systems to yield the required answers.

Continuous monitoring of pesticide residues in foodstuff is explicitly included in Regulation (EC) No 396/2005, which also requires publication of the results as a measure of risk communication to the EU population. The Annual Report on pesticide residues in food issued on a yearly basis by the EFSA (EFSA, 2011) is based on data received from 27 EU Member States and from two EFTA countries (Iceland and Norway). The EU MRL food monitoring programmes are one of the most comprehensive worldwide, covering more than 60.000 food samples every year which are analysed for up to approx. 800 different pesticides. Member States report more than 15 million determinations of pesticide residues on a yearly basis. The report also assesses the exposure of European consumers to pesticide residues through their diets.

To fill this task, analytical methods have been harmonized and standardized and method-compliant instruments, such as gas chromatograph and liquid chromatograph systems with tandem mass spectrometry identification and detection are marketed by most international suppliers of analytical chemistry instruments (Alder et al., 2006).

Risk assessment of agricultural occupational exposure (as well as for other exposures) performed in the pre-marketing phase is aimed at ensuring that a formulated active substance, when applied in the field under the conditions established as Good Agricultural Practices, is safe for use and does not pose harm to farmers' health. In real-life working conditions, however, risk assessment is seldom, if any, performed since the task has many difficulties, mainly linked to economic cost, to the limited availability of trained personnel and logistics necessary to reach small, family based enterprises, which are often poorly covered by occupational health services, to the variability of working patterns, of climatic conditions and of the frequent use of mixtures of pesticides. The existence of epidemiological studies (Baldi et al, 2001) and of case reports which suggest that chronic low-level pesticide exposure can have long-term effects on the health of agricultural workers also suggest the necessity to perform risk assessment also in 'real-life', region specific field conditions.

In the field, exposure to pesticides comes from three main routes: dermal, inhalation and oral. During open-field farming (and pesticide spraying), the contribution of the oral route is considered negligible and inhalation has been demonstrated to contribute very little to the overall exposure, while exposure by absorption from the contaminated skin (the dermal route) accounts as that quantitatively most relevant. From the point of view of risk assessment, work with pesticides can be classified into three phases, each corresponding to specific modalities of farmer exposure: preparation of the product for application (mixing and loading), spraying (application) and finally maintenance of the agricultural equipment. In each of these phases, the worker can be exposed to the pesticides to a different extent, partly by direct contact with the mixture, and partly from contact with contaminated items.

This difficulty leaves field (environmental) and biological monitoring as the most informative strategies for risk assessment. In particular, field monitoring allows to investigate how contamination builds up on operator's clothes and skin in the different phases of pesticide work in the farm including worker-to-worker variability in different ambient and organization conditions. Biological monitoring measures the dose of pesticide actually absorbed by a worker through all routes of exposure, mainly as the excretion into urine of a representative metabolite of the active substance.

What hampers a more frequent use of biological monitoring for individual risk assessment of farmers during use of pesticides is lack of reference or limit values for the interpretation of results. A pioneering approach to establish such reference has been recently demonstrated in proof-of-principle coordinated studies of farmers who sprayed herbicides (propanil) for weed control in maize cultivation (Rubino *et al.*, 2012) and of fungicides (mancozeb) on vineyards. Briefly: (***a***) health risk was calculated from comparison of internal dose to the AOEL of the active substance; (***b***) internal dose was calculated from skin dose and the skin absorption coefficient; (***c***) skin dose was assessed in a field study, along with doses on farmer's hands and clothes and with recording of employed amounts and application conditions. A (double-logarithmic) least-squares linear regression of excreted metabolite dose in urine *vs.* (the reciprocal of) health risk affords as the intercept of the equation the value of dose corresponding to absorption of a systemic dose corresponding to one AOEL, *i.e.*, the maximum allowable daily dose. Once validated, this approach can be developed into a simpler tool for risk assessment of workers exposed to pesticides and lead to the necessity to establish the Biological Exposure Index as an additional parameter requested for the regulatory authorization of Plant Protection Products.

7. Conclusions.

Considering that the use of Plant Protection Products is not deemed to be dispensed from if crop production will continue to be the staple source of humankind, strict regulation is necessary to avoid mistakes of the past, such as the use of chemically robust, bio-accumulating organics, as the frontline of pest control. Current EU regulation on the authorization of pesticides is one of the tiers of a global action aimed at improving the quality of agricultural production in the EU by protecting crops from pests with the safest active substances, used in the most rational ways to minimize unnecessary contamination of food, of the environment and health risk for the farmers.

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