



Deliverable 16:

Improved regulatory procedures for botanicals and semiochemicals and list of knowledge gaps

REBECA

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The document is based on the results of 4 workshops (Brussels, Belgium, June 13-14, 2006; Salzau, Germany, September 18-22, 2006; Brussels, Belgium, June 18-19, 2007; Brussels, Belgium, September 21, 2007) and of e-mail consultations in-between these workshops. Experts from science, regulatory authorities and industry attended the meetings and reviewed the minutes, which were used to produce this document.

Document Abstract

Adapted data requirements and regulatory procedures for «botanicals» and for «semiochemicals» are presented in separate sections. The main focus is on pragmatic improvements within the existing regulatory system under Directive 91/414. The proposals build on existing expertise such as document SANCO/10472 (botanicals) and OECD 12 (semiochemicals), and on existing knowledge on products with a long history of use. Knowledge gaps which affect the regulation of botanicals and semiochemicals are described.

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Improved regulatory procedures for botanicals

Botanicals in plant protection

Plants, and particularly plant extracts, have been used for plant protection since a long time¹. Extracts can range from crude to highly purified. In this document, the term 'botanical' is used to describe active substances made from plants. The definitions in SANCO/10472 apply (without restrictions to the range of plants and solvents). Quantitatively, the most important botanical is pyrethrum, followed by neem, rotenone and essential oils. Ryania, nicotine, sabadilla, garlic oil and *Capsicum* oleoresin have limited use². Typical uses are:

- **insecticides** (e.g. pyrethrum, rotenone, rape seed oil, quassia extract, neem oil, nicotine),
- **repellents** (e.g. neem),
- **fungicides** (e.g. laminarine, fennel oil, lecithine),
- **herbicides** (e.g. pine oil),
- **nematicides** (e.g. neem),
- **sprouting inhibitors** (e.g. caraway seed oil),
- **adjuvants such as stickers and spreaders** (e.g. pine oil) and
- **allelopathy**

Some botanicals may have more than one use.

Other use of botanicals

Plant extracts and other materials of plant origin are also used for purposes not covered by Dir. 91/414, such as

- **fertilizers and soil conditioners** (e.g. green waste compost, seaweeds and seaweed extracts, sawdust, wood chips, composted bark, bark of hemlock pine [iron micronutrient fertilizer]),
- **biocides** (e.g. pyrethrum, azadirachtin as insecticides, citronella as repellent),
- **foods and spices**. Some plant products which are mainly used as foods or spices also have a secondary use in plant protection, e.g. rape seed oil, lecithine, garlic, mustard powder, fennel and caraway. Use in plant protection is covered by Dir. 91/414, but is quantitatively minimal in comparison to use for human consumption.

Environmental impact and human health risks of botanicals

'Botanicals' covers an extremely heterogeneous group of substances, i.e. unprocessed and processed plant extracts. Furthermore, plant extracts may be highly refined (i.e. 1 active substance) or represent a 'cluster' of substances present in an extract. Characteristics of substances may be very well known (edible, traditional use, e.g. fennel oil, garlic oil, rape seed oil) or virtually unknown a priori. Extracts of plants may vary due to variability in the composition of the raw material

¹ See B.J.R. Philogène, C. Regnault-Roger and C. Vincent (2005): Botanicals: Yesterday's and today's promises. In: Biopesticides of Plant Origin, C. Regnault-Roger, B.J.R. Philogène and C. Vincent (eds), Intercept Ltd, pp 1-15.

² M.B. Isman (2006): Botanical insecticides, deterrents and repellents in modern agriculture and an increasingly regulated world. Annual Review of Entomology 51, pp 45-66.

(e.g. neem extracts) and/or due to processing/storage conditions. In conclusion, risks associated with the use of 'botanicals' may vary between very low and very high. Thus, it is extremely difficult to compile a definitive set of data requirements which would be equally applicable to all botanicals. Instead, it is proposed to compile a guidance document which explains when the data requirements of Dir. 91/414/EEC will need to be addressed by specific studies and when data requirements can be met with reasoned scientific cases («waivers»).

Regulation of botanicals and regulatory efforts

Dir. 91/414

Plant extracts or 'botanicals' are not defined in the EU legislation, and no separate data requirements exist in Directive 91/414. Data requirements can be met with studies or reasoned cases («waivers»).

Draft working document SANCO/10472

Reduced data requirements are described in the SANCO draft working document 10472³. However, this document is not legally binding. Because it has been published recently, regulators and applicants have gained only little experience with this document.

The data requirements in SANCO/10472 apply to plant protection products made from all edible parts of plants used for animal or human feed, and in addition to other parts of plants which are listed explicitly⁴. It also applies to parts of plants currently authorised as herbal drugs in European pharmacopoeia and known traditionally for plant protection properties, which are listed explicitly⁵. Further, the data requirements apply only to plant extracts made with water and/or ethanol. For plant protection products made from other plants or plant parts or with other solvents, data requirements will be established case-by-case in a pre-submission meeting, based on the available information. It is not exceptional that plant extracts are used as such. For registration purposes, the extract is therefore to be considered as the active ingredient and also as the plant protection product. Therefore, the guidance has not been separated in requirements for Annex II (active substance) and Annex III (plant protection product), but has to be interpreted on a case-by-case basis.

The document identifies two categories: Category 1: PPP made from one or several plants; category 2: PPP made from one or several plant extracts. A tiered approach is taken, where the tier 1 data requirements are explicitly described and tier 2 data can be requested on a case-by-case basis.

³ SANCO/10472/2003 – rev. 5 (6.7.2004). Draft working document concerning the data requirements for active substances of plant protection products made from plants or plant extracts.

⁴ artichoke (edible parts), basil (whole plant), black pepper (fruit), carvi (fruit), chives (clove), coriander (fruit), elder (bark, flower, fruit), garden sage (whole plant), garlic (clove), horse tail (leaf), laurel (leaf), mint (whole plant), olive (oil), onion (bulb), oil seed-rape (oil), sesame (seed), soybean (oil), squash (seed), sunflower (oil), tomato (fruit)

⁵ bladder wrack (thallus), feverfew (whole plant), lavender (whole plant), nettle (whole plant), rhubarb (rhizome only), sweet chamomille (whole plant)

Low-risk and basic substances

The proposed new Regulation⁶ on plant protection products contains special requirements for «low risk active substances» and for «basic substances». These are relevant for a number of botanicals. The proposal does not specify how a low risk substance is identified but it is intended to be the result of a full risk assessment. Low risk active substances are approved for longer periods than other substances (Art. 22), and products based on low risk active substances are authorized within short periods (Art. 46).

Basic substances are defined as active substances which (i) are not predominantly used as a plant protection product but (ii) nevertheless have some use as a plant protection product, either directly or in a product consisting of the substance and a simple diluent, (iii) are not substances of concern, and (iv) are not directly marketed for use as plant protection products. Examples could be rape seed oil, garlic oil, fennel oil, caraway seed oil, lecithine or essential oils.

Plant strengtheners

Plant strengtheners are not specifically regulated at EU level. There have been attempts to define data requirements for plant strengtheners with low risk profile (SANCO/1003/2000 rev. 3). However, these activities have been discontinued.

Minimal Risk Pesticides

In the USA, there is a list of substances that can be used as pesticides without any registration. These substances are called Minimal Risk Pesticides, the list is known as «25b list». The list contains many essential oils. All inerts must be on EPA's 4A inert list, all ingredients must be identified on the label, and the label may not contain false or misleading claims. Currently, the 25b list includes, among others, the following botanicals: castor oil, cedar oil, cinnamon and cinnamon oil, citric acid, citronella and citronella oil, cloves and clove oil, corn gluten meal, corn oil, cottonseed oil, eugenol, garlic and garlic oil, geraniol, germanium oil, lauryl sulfate, lemongrass oil, linseed oil, malic acid, mint and mint oil, peppermint and peppermint oil, rosemary and rosemary oil, sesame (includes ground sesame plant) and sesame oil, sodium lauryl sulfate, soybean oil, thyme and thyme oil and white pepper.

In Australia, the following plant extracts are excluded from the requirements of AVPMA approval as constituents in plant protection products: Cabbage extract, Canola oil, Capsicum oleoresin, Chilli extract, Citronella oil, Cypress wood oil, Derris dust, Eucalyptus oil, Garlic extract, Garlic oil, Lanolin oil, Lavender fragrance, Lime oil, Orange oil, Pine oil, Pyrethrins, Pyrethrin I, Pyrethrin II, Quassia, Rotenone, Salicylic acid, Sesame, Tea tree oil and Thymol.

Substances of low concern

The Commission (DG SANCO) is currently working on a new regulation which will contain criteria for identifying active substances of 'low concern'. These criteria are not specifically made for botanicals, but it is likely that some botanicals will fulfil them. Particularly for substances which are used as food or feed, it can be assumed that certain criteria are met. The criteria will be applied after evaluation by the RMS and are therefore not relevant for dossier preparation.

⁶ Proposal for a Regulation of the European parliament and of the Council concerning the placing of plant protection products on the market. 2006/0136 (COD), 12.7.2006

Discussions in the REBECA project

Workshop 'botanicals' on 13 – 14 June 2006

The participants of the workshop held on 13 – 14 June 2006 concluded that

- 'Botanicals' are an extremely heterogeneous group with great variation in potential risks. Risks should therefore be assessed case-by-case, and the discrimination of low risk substances from other substances should be the result of an assessment.
- Characterization of the «active substance» is more difficult for botanicals than for synthesized chemical substances.
- SANCO/10472 provides a useful basis for developing adequate data requirements.

Workshop 'botanicals' on 18 – 22 September 2006

The participants of the workshop held on 18 – 22 September 2006⁷ concluded that

- For extracts containing clusters of substances, guidance on specification should be provided. Purification of extracts should be encouraged.
- SANCO/10472 is a valuable approach. It should be amended by including other methods of extraction, and by specifying the terms 'product' and 'extract'. The list of plants in the Annex should remain indicative.
- The registration of low risk botanicals should be facilitated.
- The registration requirements for botanicals used as plant protection products and as biocides should be harmonized.
- «Waivers» (=substitution of studies by reasoned cases / justification of non-submission of data) are an important instrument to reduce studies for data requirements considered unnecessary in particular cases.
- 'Botanicals' are defined by origin from plant material, and not by mode of action (which is known in some cases and unknown in others). The definition is based on the origin of the active substance or cluster of substances, and is independent from the origin of inerts which might be added to products.
- Further research was suggested concerning identification and quantification of components of plant extracts, identification of new active substances, identification of new uses and resistance management. The 'dossier-relevance' of publicly funded research should be improved.

⁷ Download of minutes: <http://www.rebeca-net.de/downloads/REBECA%20Documents/Group%20work%20botanicals/Minutes%20Botanicals.pdf>

Workshop 'botanicals' on 18 – 19 June 2007

The participants of the workshop held on 18 – 19 June 2007 reviewed the preliminary proposals and suggested improvements.

Workshop 'botanicals' on 21 September 2007

The participants of the workshop held on 21 September 2007 reviewed the draft proposals and suggested minor improvements.

Questionnaire on 'low risk' substances

Regulators, industry, consultants and academia were asked to fill in a questionnaire on 'low risk' products. Opinions varied greatly regarding definition/criteria for low risk substances, as well as possible examples within botanicals. Typical statements were that low-risk substances should be easily degradable/non-persistent, known from human nutrition or used for a long time without any record of negative effects on humans, wildlife, or the environment.

When discussing individual substances with a history of safe use, there were often disagreements whether or not this substance can be regarded as 'low risk substance'. It must be emphasized that plant protection products could present different categories of risks (mainly risks for workers and bystanders; for consumers; for the environment). The history of safe use may demonstrate low risk with respect to a certain risk, but may be irrelevant for other risks. Thus, it may be used to «waive» some, but not all data requirements on human health and the environment. For example, use as food justifies the non-submission of data on oral toxicity, but not necessarily on skin irritation. A substance can only be considered as low risk substance, if all its risks are low.

A priori versus a posteriori evaluation of 'low risk' properties

Regulators have pointed out that according to the precautionary principle, an assessment is needed to determine whether a substance is 'low risk'. For botanicals, the normal data requirements would therefore apply. Under the proposed new Regulation on plant protection products, low risk active substances are approved for longer periods than other substances (Art. 22), and products based on low risk active substances are authorized within short periods (Art. 46).

To achieve the goals of the REBECA project for botanicals, a system is required in which the low risk properties of a substance can be identified prior to the full risk assessment, in order to save the generation of unnecessary data.

Botanicals in the 4th stage of review

Many botanicals are subject to re-evaluation under the 4th stage of the review programme under Directive 91/414, for example azadirachtin, pyrethrins, rape seed oil and quassia. Many of these botanicals have been used in plant protection for many years, without evidence of adverse effects on human health. In most cases,

there are very little experimental data on human health effects available. At the moment, it is difficult to predict the outcomes of the 4th stage of review for botanicals.

Proposed data requirements for Annex I inclusion of botanicals and for registration of plant protection products based on botanicals

REBECA Proposals concerning a guidance document for botanicals

The REBECA project recommends that a comprehensive guidance document should be formally adopted for botanicals. This could be based on SANCO/10472, with some amendments. Certain amendments can already be proposed at this stage. After completion of the 4th stage, it may be possible that further amendments can be proposed.

REBECA Proposals concerning the further development of SANCO/10472

The REBECA project recommends that the scope of SANCO/10472 is broadened.

- Currently, SANCO/10472 covers only water and ethanol extracts. Its scope should be broadened to cover all extraction methods.
- Currently, SANCO/10472 lists only a limited number of plant parts in the annex. Its scope should be broadened to cover all plants and plant parts.
- As a result of the broadened scope of plants and extraction methods, a tiered system will be needed. It is desirable to establish a system to identify substances/extracts of low risk/concern at an early stage of the process. For these substances, only tier I data requirements apply.
- The document should contain a list of plants and/or combinations of plants and extraction methods which are recognized as of low risk/concern. This should be an open list which can be amended when new botanicals have been evaluated (taking into account issues of data protection).
- As a starting point, all substances which are currently listed in SANCO/10472, all substances on the «25b list» of the US EPA and all substances with GRAS status should be considered for such a list. For this task, support by an EU funded research project would be useful.

OECD Section 1, Chemical Properties

Plants contain a multitude of chemical substances, and the same is true for plant extracts (e.g. water and ethanol extracts), unless if they are highly purified. One or several substances may be active against the target pest, one or several substances may present a hazard to human or animal health or the environment, and many other substances have neither effect.

Often, the «active substance» is a cluster of very similar substances. For example, pyrethrum contains three esters of chrysanthemic acid and three esters of pyrethric acid. Of these, pyrethrin I and II are the most abundant and account for most of the insecticidal activity. Neem contains more than a dozen azadirachtin analogues, but the major form is azadirachtin, and the other analogues contribute little to overall efficacy. Neem also contains other triterpenoids such as salannin, nimbin, and derivatives thereof. Their role has been

controversial, but seems to be minor in comparison to azadirachtin⁸. In conclusion, it is often not possible in botanicals to draw a clear line between active and inactive substances. However, it is usually possible to identify one or a few substances which are responsible for most of the activity of the extract.

In contrast to synthetic pesticides, plant extracts almost inevitably contain a large array of highly diverse substances which are hardly or not at all responsible for the effect on the target pest. In terms of Dir. 91/414, they are considered as «by-products» or «impurities». If they are present in quantities ≥ 1 g/kg in the active substance as manufactured, they are considered as «significant impurities». If they are of toxicological and/or ecotoxicological or environmental concern, they are considered as «relevant impurities» (see Annex IIA, Point 4.). Sometimes, there is a lack of knowledge as to which the active components of an extract are.

Two groups of substances may present a hazard to human or animal health or the environment: (i) certain plant metabolites with high toxicity⁹, and (ii) microbial metabolites or decay products which may be formed before and during manufacture¹⁰ and (iii) process impurities. The presence of other plant metabolites is unavoidable (except if they can be eliminated by purification), while microbial contaminants and process impurities can be avoided with appropriate quality management.

Dir. 91/414 requires identification of each component, present in quantities of 1 g/kg (see Annex IIA, Point 1.10). Botanicals may be composed of:

- one or several **active substances**,
- **plant constituents of concern**,
- **impurities** and
- **other plant constituents** (e.g. sugars, fatty acids, terpenoids).

The aim of this proposal is to ensure constant quality and composition of plant extracts. According to the current data requirements in Dir. 91/414, this aim is achieved by analysing all lead substances and relevant plant constituents and 'impurities' with validated methods. This causes very high costs. Therefore, an alternative approach is proposed here for botanicals, which will reduce the need for validation of all significant/non-relevant 'impurities' and will improve quality control of botanicals:

To verify the quality of the plant extract, representative parameters (e.g. sum parameters such as sugars, fatty acids, terpenoids, pH) should be identified and monitored. These should mirror the production and extraction process and adequately reflect the constant quality of the production process and indicate deviations which may lead to unforeseen relevant impurities in the technical active substance.

REBECA Proposals concerning identification and analytical methods

Identification and analytical methods shall be required for the active substance(s), or for those substances which are mainly responsible for the effects on the target pest. If these are not identified, it should be determined case-by-case whether one or several representative lead substances (markers) may be used instead.

Identification and analytical methods shall further be required for all impurities of concern, and for all plant constituents of concern (= 'relevant impurities' sensu Dir. 91/414, Annex IIA, Point 4).

⁸ M.B. Isman (2006): Botanical insecticides, deterrents and repellents in modern agriculture and an increasingly regulated world. Annual Review of Entomology 51, pp 45-66.

⁹ E.g. alkaloids, terpenes, glycosides

¹⁰ E.g. mycotoxins

The other plant constituents should be characterized (e.g. by group analysis for sugars, fatty acids, terpenoids), but identification and validated analytical methods are not required for each component present in quantities ≥ 1 g/kg (=‘significant impurities’ *sensu* Dir. 91/414, Annex IIA, Point 4).

It is not feasible to achieve 98% of closure as required in conventional pesticides. However, the relevant components should be identified as far as necessary in order to ensure reproducibility of the product (on a case-by-case base). For example, the threshold for ‘significance’ could be considered to be raised.

Where possible and necessary, purification of plant extracts should be encouraged.

The content of metabolites in plants is subject to great quantitative and sometimes also qualitative variation. Variation occurs between different plant parts, different physiological ages, different harvesting times, different growing conditions (e.g. nutrient, water or light availability), different regions and different genotypes. Due to this variability in the material of origin, the contents of the active substance(s) in plant extracts usually varies also to some extent.

REBECA Proposals concerning the description of manufacturing methods (material of origin)

The description of the method of manufacture (Point 1.8) should include information on the plant material of origin, such as the plant parts used, the physiological ages, harvesting times, growing conditions (e.g. nutrient, water or light availability), regions and genotypes/chemotype (if known), and should indicate the range of materials used. The plant material should be produced by sustainable methods and the Rio convention on biological diversity must be respected. In view of the great variability in plants, the applicant is free to define terms such as «growing conditions» and «region», based on the biology and distribution of each plant species. It is advised that applicant and evaluator agree on this in a pre-submission meeting. If other plant material of origin is used in the future, the applicant has to demonstrate equivalency of the technical material with the criteria outlined here. If the supplier of the plant extract does not want to disclose this information to the manufacturer of a plant protection product, the regulatory authority may obtain the information directly from the supplier.

The range of samples to be analyzed (region, genotype/chemotype, age, harvesting time, growing conditions and replicates) should be agreed in a pre-submission meeting. As a minimum, the analytical profile of batches (Point 1.11) must be based on five samples and cover the harvest from at least two years.

Greater variation in the composition should be acceptable for botanicals than for synthetically produced substances.

If plant material or extracts are stored inappropriately, hazardous microbial decay products may be formed during manufacture, e.g. mycotoxins.

REBECA Proposals concerning the description of manufacturing methods (HACCP)

The description of the method of manufacture (Point 1.8) should include all measures taken to prevent the formation of hazardous microbial decay products during manufacture (according to HACCP procedures). The description should cover harvesting, storage and transport of plant material, manufacture and storage of the plant protection product.

If the formation of hazardous decay products/microbial contamination is expected to occur in the materials of origin, analytical/microbiological data for these substances have to be provided under Point 1.10 and 1.11.

REBECA Proposals concerning application and use

With respect to application and use of botanicals, the approach of SANCO/10472 should be followed.

OECD Sections 3 – 6, Human Health; Residues; Fate and behaviour in soil, water, air; effects on non-target organisms

Botanicals differ from synthetic plant protection products in the following ways:

- They have always been present in natural environments (although not necessarily in the same quantities and purity).
- Some are rapidly and completely metabolized in the environment. For example, pyrethrins have an outdoor half-life of 2 hours or less, and azadirachtin has a half-life of a few days¹¹. Rapid and complete degradation is a very good argument to «waive» residue and environmental fate and behaviour studies.
- Many plants and plant extracts are extensively used for purposes other than plant protection (e.g. food, feed, fragrances, flavourings, pharmacopoeia), without evidence of adverse effects ('history of safe use').
- Many botanicals currently in the 4th stage of re-evaluation have a long history of safe use as plant protection products.

Note: The legislation relating to medicinal products for human use¹² establishes a simplified registration procedure ("traditional-use registration") for herbal medicinal products which fulfil certain criteria (Art. 16a, para 1). The substance must have been in use for at least 30 years, and at least 15 years within the Community (Art. 16c, para 1 (c)).

REBECA Proposals concerning the identification of low risk/concern substances

The REBECA project recommends a system in which botanicals of low risk/concern are identified **early in the process**, and are subject to reduced data requirements. Substances with a history of safe use in plant protection or for other purposes shall be considered as 'low concern' substances.

REBECA Proposals concerning risk assessment

If a plant extract has been used in plant protection or for other purposes without evidence of adverse effects, its history of safe use shall be adequately taken into account. This includes the use of information from the literature and from other public sources, and its history of safe use. Details of a 'safe use' such as the concentration and level of exposure have to be considered. Which data requirements can exactly be fulfilled by such data should be determined in a pre-submission meeting. Bridging of information from similar extracts should be encouraged, but the relevance must be justified by the applicant in each case.

The following table provides some guidance how safe use should be considered in risk assessment. Applicants should provide reasoned cases based on exposure, dose, natural background levels, and application pattern:

¹¹ According to discussions at the REBECA workshop on botanicals held on 19.6.2007.

¹² Council Dir. 2001/81, amended by Council Dir. 2004/24

Safe use in ...	May provide justifications to replace some or all studies in the following areas:
Human nutrition	oral toxicity, residue studies
Animal feeding	oral toxicity, residue studies
Cosmetics	dermal irritation/sensitization, oral toxicity
Agriculture (e.g. fertilizers)	ecotoxicology, environmental fate (needs to be verified case-by-case)
Occurrence in nature (e.g. nettle)	ecotoxicology, environmental fate (needs to be verified case-by-case)
Pharmacopoeia*	must be determined case-by-case
Biocide	must be determined case-by-case
Technical use	must be determined case-by-case
* called «traditional use» in this context	

OECD Section 7, Efficacy data

The use of botanicals can involve specialized techniques, which require modification of trial protocols (e.g. plot size, replicates). Authorities should accept modified trial protocols, but it is important that the rationale for the trial protocol is justified by the applicant. Botanicals may be more variable in their performance than conventional chemical pesticides, but provided a demonstrable and consistent benefit is achieved, approval can still be acceptable. The product label should accurately reflect the levels of performance that may be expected, as well as provide guidance on how to achieve these.

REBECA Proposal concerning efficacy evaluation (flexible trial protocols)

Requirements for efficacy data should be flexible.

REBECA Proposal concerning efficacy evaluation (minor beneficial effects)

Even products with only minor beneficial effects should be acceptable, provided that it is reproducible and the label accurately reflects the likely benefits.

REBECA Proposal concerning efficacy evaluation (guidance for efficacy evaluation)

Introduction of efficacy into EU evaluation needs to be accompanied by appropriate guidance on evaluation criteria.

REBECA Proposal concerning selectivity tests

Selectivity tests should be included in efficacy tests.

Improved regulatory procedures for semiochemicals

Semiochemicals in plant protection

Semiochemicals are chemicals emitted by plants, animals, and other organisms – and synthetic analogues of such substances – that evoke a behavioural or physiological response in individuals of the same or other species. They include pheromones and allelochemicals. Pheromones modify the behaviour of other individuals of the same species, while allelochemicals act on different species.

Most semiochemicals used in plant protection products are «straight-chained lepidopteran pheromones» (SCLPs). They have their natural function as sexual pheromones. They are produced and released by female Lepidoptera to attract («call») males for mating. Males are able to find females over relatively long distances, using the concentration gradient of the pheromone in the air. In the «mating disruption» technique, the pheromone is artificially applied in excess, so that no gradient from a calling female can be built up. Therefore, males are no longer able to find females, resulting in unfertilized females and a reduction in offspring. Besides mating disruption, semiochemicals can also be used for mass trapping, monitoring and «attract & kill». In mating disruption and mass trapping, semiochemicals are considered as pesticides. In monitoring and attract & kill, they are not considered as pesticides, and are therefore exempt from registration.

Semiochemicals present a particular case among active ingredients used in plant protection products, as they are the only pesticides not intended to kill the pest organism. Semiochemicals have a high specificity for the target species.

Environmental impact and human health risks of semiochemicals

The OECD 12 consensus document¹³ provides the following rationale for reduced data requirements: Semiochemicals are generally effective at very low rates, comparable to levels that occur naturally. They are generally volatile and usually dissipate rapidly in the environment. In addition, many end use products are formulated in passive dispensers (hollow fibres, tapes) that present little direct exposure to humans and non-target organisms. Furthermore, they are usually not directly applied to the crop. In this case, exposure is limited to localised areas where the dispensers are placed (note: exposure may be higher in the case of direct application). All these factors minimise the risk of adverse effects from the use of semiochemicals. OECD no 12 concludes that SCLPs in particular have a low toxicity, and that arthropod semiochemicals in general have a low exposure potential.

- SCLPs are of low toxicity to mammals.

¹³ Guidance for Registration Requirements for Pheromones and Other Semiochemicals Used for Arthropod Pest Control. OECD Environment, Health and Safety Publications Series on Pesticides No. 12. ENV/JM/MONO(2001)12.

- The application rate is typically low and probably comparable to natural emissions.
- Volatility and rapid environmental transformation minimise residues in crops and exposure of non-target organisms.

These findings have been supported by experience of the US EPA, resulting in a recent proposal for relaxed registration requirements for semiochemicals¹⁴. The REBECA project anticipates that these findings will also be supported by the 4th stage re-evaluation.

Annex I inclusion of 'old' pheromones

Semiochemicals in the 4th stage of review

A number of semiochemicals are subject to re-evaluation under the 4th stage of the review programme under Directive 91/414. The Rapporteur Member State is Austria. Among these, the 'straight-chained lepidopteran pheromones' (SCLPs) make up a very homogenous group of substances. Not only single substances were notified, but also blends of substances. Most of the SCLPs were notified with the 'single evaluation dossier' prepared by the IBMA¹⁵ task force. Here, the semiochemicals supported by IBMA are listed as examples.

SCLP acetates notified as single substances:

- 5-decen-1-yl acetate
- (E)-8-dodecenyl acetate
- (E/Z)-8-dodecenyl acetate
- (Z)-8-dodecenyl acetate
- (Z)-9-dodecenyl acetate
- (7E, 9Z)-dodecadien-1-yl acetate
- (E)-11-tetradecenyl acetate
- (Z)-9-tetradecenyl acetate
- (Z)-11-tetradecenyl acetate
- (9Z, 12E)-tetradecadien-1-yl acetate
- (Z)-11-hexadecen-1-yl acetate
- (Z)-13-hexadecen-11-ynyl acetate
- (7Z, 11E)-hexadecadien-1-yl acetate
- (2E, 13Z)-octadecadien-1-yl acetate
- (Z,Z,Z,Z)-7,13,16,19-docosatetraen-1-yl isobutyrate

SCLP alcohols notified as single substances:

- 5-decenol
- (Z)-8-dodecenol
- (E, E)-8,10-dodecadien-1-ol
- 1-tetradecanol

¹⁴ Federal Register, Part III, Environmental Protection Agency, 40 CFR Parts 158 and 172, Pesticides; Data Requirements for Biochemical and Microbial Pesticides; Proposed Rule, March 8, 2006

¹⁵ IBMA = International Biocontrol Manufacturer's Association

- (Z)-11-hexadecen-1-ol

SCLP aldehydes notified as single substances:

- (Z)-7-tetradecenal
- (Z)-9-hexadecenal
- (Z)-11-hexadecenal
- (Z)-13-octadecenal

Blends of SCLP acetates (these SCLPs were only notified as components of blends):*

- (Z)-8-dodecenyl acetate & dodecan-1-yl acetate*
- (Z)-9-dodecenyl acetate & dodecan-1-yl acetate*
- (7E, 9Z)-dodecadienyl acetate & (7E, 9E)-dodecadienyl acetate*
- (7Z, 11Z)-hexadecadien-1-yl acetate* & (7Z, 11E)-hexadecadien-1-yl acetate

Blends of SCLP aldehydes:

- (Z)-9-hexadecenal; (Z)-11-hexadecenal & (Z)-13-octadecenal

Blends of different SCLPs:

- 5-decen-1-yl acetate & 5-decen-1-ol
- (E/Z)-8-dodecenyl acetate & (Z)-8-dodecenol
- (Z)-11-hexadecenal & (Z)-11-hexadecen-1-yl acetate

Other semiochemicals:

- 1,4-Diaminobutane (Putrescine)

Listing of SCLPs in Annex I of Dir. 91/414

The REBECA project anticipates that the 4th stage of review will demonstrate that all evaluated SCLPs have similar, very low environmental impact and human health risks, and can therefore be included in Annex I of Dir. 91/414. Theoretically, the listing is possible in different ways.

1. «Straight-chained lepidopteran pheromones» could be listed collectively. This possibility is most favourable for the development of new pheromone products. It facilitates the registration of products based on SCLPs which are already listed, as well as new SCLPs, which could be registered according to the rules for «equivalence of technical material». Of course, data protection must be ensured. However, some regulators fear that this might set an unwanted precedent for certain chemical substances such as pyrethroids, triazoles or sulfonylurea. Note: Under the new pesticides directive, active substances have to be re-evaluated 10 years after Annex I inclusion (15 years for low risk substances). In the case of collective listing, it needs to be clarified how this provision is implemented. On 15 May 2007, the Standing Committee decided to take such an approach for baculoviruses. New isolates would be

applied for at MS level, and would require an Annex II and III dossier. The main part would refer to the existing DAR.

2. Chemically similar subgroups of the SCLPs could be listed collectively, e.g. «SCLP acetates», «SCLP alcohols» and «SCLP aldehydes». These subgroups are chemically similar to each other and there is no indication that one of these subgroups needs to be regulated differently from the other subgroups. Therefore, this option has no advantages over option 1.
3. Each substance could be listed separately.
4. In the case of blends, each component of the blend could be listed separately (=2.), or the blend could be listed as a whole. This possibility is the least favoured by the industry, because it hinders the development of new end-use products based on new blends of pheromones which are already listed.

Rationale for collective listing of all SCLPs: the arguments for reduced data requirements given in OECD 12 are also valid for other SCLPs.

- Because of structural similarity, new SCLPs are likely to be of similarly low toxicity to mammals as old SCLPs.
- Volatility and rapid environmental transformation minimise residues in crops and exposure of non-target organisms.
- The proposal should be limited to SCLPs applied at <375 g/ha. Such application rates are low and probably comparable to natural emissions. For SCLPs applied at >375 g/ha, see proposals below.
- These proposals would harmonize EU regulation with the US EPA's proposed new rule.

REBECA proposal concerning listing as SCLPs in Annex I

In case of positive evaluation in the 4th stage, SCLPs should be listed collectively in Annex I, as described above under option 1.

SCLPs are low risk substances

The proposed new pesticides Regulation¹⁶ contains some facilitations for «low risk active substances» (Art. 22 and 46).

REBECA proposal concerning 'low risk' status of SCLPs

When the new pesticide Regulation is in force, all SCLPs should be treated as low risk substances. Clarity and predictability of low risk status would benefit all sides and would lead to cost and time reductions for all parties.

Note: This proposal reflects the current opinions, but will depend on the finalised and agreed definition of «low risk» in the revised Directive, and on the outcome of the re-evaluation of the SCLPs.

¹⁶ Proposal for a Regulation of the European parliament and of the Council concerning the placing of plant protection products on the market. 2006/0136 (COD), 12.7.2006

Proposed data requirements for Annex I inclusion of new semiochemicals and for registration of plant protection products based on semiochemicals

OECD Section 2, Analytical Methods

In the case of SCLPs, two types of impurities occur, (i) other SCLPs and (ii) unrelated contaminants. Other SCLPs are typically stereo-isomers of the active substance, or closely related molecules which differ from the active substance in the position/orientation of a double bond, alcohol, acetate or aldehyde group. These result mainly because a small proportion of the material does not undergo the synthetic pathway completely. There is no indication that these substances are of toxicological concern and if present in low quantities, they do not adversely affect efficacy (in mass trapping, higher purity may be needed than in mating disruption). Because of their chemical similarity, removal of other SCLPs is neither economically feasible nor necessary.

Unrelated contaminants may be of toxicological concern, and they may affect effectivity. Manufacturers use HACCP procedures to avoid the formation of other contaminants. Information on the manufacturing process is likely to be useful to identify the potential for the formation of substances of toxicological concern.

Dir. 91/414 requires identification of each component present in quantities of 1 g/kg (=0.1 %) (Annex IIA, Points 1.10 & 1.11), and validated analytical methods for the detection of these impurities (Point 4.2.3).

REBECA Proposal concerning analysis of impurities

Information on the manufacturing process shall be used to determine the likely identity of impurities. For impurities which are SCLPs or structurally similar substances, validated analytical methods shall only be required if they are present in quantities ≥ 20 g/kg. For other impurities, validated analytical methods shall be required if they are present in quantities ≥ 1 g/kg.

Dir. 91/414 requires analysis of «representative samples» of the active substance (Annex IIA, Point 1.11). According to the survey in OECD 12, analyses from 5 batches are requested in the EU if feasible, while only 3 are requested in the USA, Canada and Switzerland¹⁷. For some pheromones not produced every year, multiple analyses are nothing else than pseudo-replicated analyses of same sample.

REBECA Proposal concerning the number of samples to be analyzed

For rarely produced pheromones (e.g. 1 batch/3 years), it should be acceptable to present results from fewer batches (down to 1) and the manufacturing process (as opposed to 5 batches, which is normally required). In this case, additional analyses must be provided as soon as additional batches have been manufactured. This approach must be justified by the applicant. Comment: one regulator stated that this is already their current practice.

¹⁷ See OECD 12, Appendix 1

OECD Sections 3 – 6 (Human health; Residues; Fate and behaviour in soil, water, air; Effects on non-target organisms)

The REBECA project proposes the following facilitations in line with OECD 12 and with the US EPA's new proposed rule for biopesticides.

REBECA Proposal concerning risk assessment of SCLPs

If SCLPs are used in quantities comparable to natural emission (up to 375 g/ha per year) no data shall be required for OECD sections 3 – 6 (human health; residues; fate and behaviour in soil, water, air; effects on non-target organisms). Note: This is relevant for most current applications of SCLPs.

If SCLPs are used in quantities higher than natural emission or above 375 g/ha per year, data may be required for OECD sections 3 – 6 (human health; residues; fate and behaviour in soil, water, air; effects on non-target organisms) case-by-case.

Other semiochemicals

SCLPs have been intensively studied and are widely used in plant protection. The currently available knowledge shows that the lepidoptera have pheromones with very similar structure and function, and with very similar safety profiles.

The pheromones of other arthropods are much less studied. Nevertheless, several other taxonomic groups of arthropods also have pheromones which are structurally very similar within one taxonomic group, e.g.:

- beetles (coleoptera): pheromones based on terpenoids,
- midges (a group of flies; diptera): pheromones based on diacetoxy alkanes,
- pentatomides (a group of bugs; heteroptera): pheromones based on alkene esters.

The REBECA project assumes that many of these pheromones have similar safety profiles as the SCLPs, and suggests relaxed registration requirements, as soon as this assumption is confirmed. At the moment, these pheromones are not well known from a regulatory point of view, and have to be evaluated on a case-by-case basis. With increasing experience (i.e. when ca 3 – 5 products have been registered), however, these pheromones could be regulated in a more generic way, comparable to that suggested above for SCLPs. In this case, the issue of data protection would have to be resolved¹⁸. The REBECA project therefore makes two proposals: one for evaluation at the present time, and another proposal for evaluation when more experience is available.

¹⁸ The industry is discussing a system in which the money paid for access to protected data for SCLPs is retained in a fund which can be used to finance the registration of «pioneer substances» of a new group of pheromones. As soon as this group of substances reaches the status at which it can be considered more generically, it would itself generate payments, which could then be used for the next group of pheromones.

REBECA Proposals concerning risk assessment of other semiochemicals

For the moment, the following data requirements shall be used:

- OECD sections 3 & 4 (human health; residues): Data requirements shall be determined case-by-case in a pre-submission meeting, taking into account natural emissions and the history of exposure to the substance.
- OECD sections 5 & 6 (fate and behaviour in soil, water, air; effects on non-target organisms): If application rates are comparable to natural emissions, no data shall be required. Otherwise, data requirements shall be determined case-by-case in a pre-submission meeting, taking into account natural emissions.

As soon as 3 – 5 structurally similar semiochemicals are listed on Annex I, the Commission and the RMSs for these semiochemicals shall decide whether the number of substances and their similarity is sufficient to justify a more generic approach. If they agree to take a generic approach and if these semiochemicals have been found to have a low risk profile (e.g. similar to SCLPs), the following approach shall be used:

- No data shall be required for OECD sections 3 – 6 (human health; residues; fate and behaviour in soil, water, air; effects on non-target organisms).
- Each new group of structurally similar semiochemicals shall be listed collectively in Annex I.
- It shall be explored whether it is necessary and possible to make similar relaxations concerning the analysis of impurities as those proposed for SCLPs in this document.

OECD Section 7, Efficacy data

The use of semiochemicals can involve specialist techniques, which require adapted trial protocols. Authorities should not be too prescriptive concerning trial protocols, but it is important that the rationale for the trial protocol is justified by the applicant. Pheromones applied in dispensers need to be applied to large areas and therefore, the requirement for crop destruction would cause very high costs (ca 160'000 EUR per trial), which would effectively preclude doing a trial.

REBECA Proposal concerning efficacy evaluation (flexible trial protocols)

Requirements for efficacy data should be flexible and adapted to the special properties of semiochemicals. For pheromones used in mating disruption and autoconfusion, PSD efficacy draft guideline 220 on mating disruption products could be used as a guideline (note: an EPPO standard based on this guideline is under work). It is also recommended to develop EPPO guidelines for evaluation of mass trapping.

If semiochemical products are not directly applied to crops, there should be no requirement for crop destruction. If they are applied directly to crops, discussion regarding crop destruction is needed.

Semiochemicals acting through mating disruption do not directly affect the population size of the treated generation, but rather affect the following generation. Therefore, a comparison with chemicals for short-term effects on population size is not appropriate. Evaluation and approval may be based largely on demonstrating a reduction of crop damage. Long term effects accumulating over several seasons could also be taken into account, and information on factors such as numbers of overwintering larvae provide very useful support on the longer term effects. Even if these effects are frequently observed, they are difficult to quantify. However, the label should reflect what benefits the grower may expect, and have clear directions on the optimum use of the product.

REBECA Proposal concerning efficacy evaluation (minor beneficial effects)

Products with minor beneficial effects should also be acceptable, provided that they can be demonstrated and the label accurately reflects the observed benefits.

REBECA Proposal concerning efficacy evaluation (data from other areas)

Efficacy data from all areas of the EU or from outside the EU should be acceptable, if they have been generated under comparable conditions. The use of efficacy data from all areas of the EU and, where relevant, also outside the EU, should be actively encouraged (e.g. by mutual recognition). This will avoid unnecessary repetition of efforts, but also acknowledges the practical difficulties in designing such trials (e.g. the need for large plot sizes and often impracticalities of having replicated treatments). Reasoned cases justifying the comparability of such data should be based on issues such as pest biology, climatic conditions, number of generations, formulations and label claims, and must take into account potential differences in agricultural practices, average field size, and shape and size of trees/vines.

Harmonization of registration for semiochemicals

In the working group of semiochemicals, some applicants reported the experience that the registration of pheromones as biocides is far more expensive than the registration as PPP. This is due to higher registration fees and to lesser flexibility (e.g. SCLPs cannot be submitted in a joint dossier). This issue is also addressed in the «proposals for improvement of the EU regulation and registration process for BCAs».

REBECA Proposal concerning registration of semiochemicals

REBECA asks that the registration requirements for semiochemicals used particularly as biocides, but also for human and veterinary medicine are harmonized with those for PPP. In particular, joint dossiers should be permitted for the inclusion on Annex 1 & registration of SCLPs, and the registration fees should be lowered proportionately to the volume of work necessary.

Knowledge gaps

Knowledge gaps in botanicals

The development of botanicals which are sufficiently active is extremely tedious and takes a lot of resources. Efficient botanicals have been developed for the control of important pests and diseases. However, it will require a massive effort in the future to identify further products that control all key pests and diseases and to bring these products on the market. R&D efforts are still very small in comparison to what is really needed in the future for such products. It is therefore recommended to continue and intensify publicly funded research activities (in public research facilities as well as in the industry) to further facilitate the development of these products.

REBECA proposes to broaden the scope of SANCO/10472, to include extracts from all plants and all extraction methods (see above). The document should contain a list of plants and/or combinations of plants and extraction methods which are recognized as of low risk/concern. REBECA also proposes that substances of low risk/concern should be identified early in the registration process, and be subject to reduced data requirements.

There is no agreed definition of 'low risk' which could be used in the context of regulation of botanicals. At the moment, it is not clear which botanicals can be regarded as being of low risk/concern. At the workshop on 19 June 2007, the following approach to fill this knowledge gap was identified:

1. The list of plants and/or combinations of plants and extraction methods which are recognized as of low risk/concern should be an open list which can be amended when new botanicals have been evaluated (taking into account issues of data protection).
2. As a starting point, all substances which are currently listed in SANCO/10472, all substances on the «25b list» of the US EPA and all substances with GRAS status should be considered for such a list.
3. The experience gained in the evaluation of botanicals during the 4th stage of re-evaluation should be utilized.
4. The participants at the workshop on 19 June 2007 welcomed this approach, but stated that none of them have the capacities to do this job on their own. Therefore, support by an EU funded research project was judged to be highly useful.

Besides the botanicals, there are other presumable low risk/concern substances which can be used for plant protection (e.g. substances of animal origin such as lactoperoxidase, rock powder, potassium bicarbonate). These substances were out of the scope of the REBECA project. At a very late stage in the REBECA project, IBMA has made a proposal that the relaxations elaborated for botanicals should be extended to «biochemical substances (including botanicals)» (see letter annexed to this document). This proposal came too late to be fully discussed with all stakeholders and incorporated into the REBECA proposals.

REBECA suggests that a follow-up project should discuss whether the REBECA proposals for botanicals can be extended to other substances, and elaborate the necessary amendments to the proposals.

Knowledge gaps in semiochemicals

SCLPs have been intensively studied and are widely used in plant protection. The currently available knowledge shows that this taxonomic group of arthropods (=the lepidoptera) has pheromones with very similar structure and function, and with very similar safety profiles. No major knowledge gaps were identified with respect to SCLPs.

By contrast, major knowledge gaps were identified with respect to non-lepidopteran pheromones and other semiochemicals. The pheromones of other arthropods are much less studied. Nevertheless, several other taxonomic groups of arthropods also have pheromones which are structurally very similar within one taxonomic group, e.g. beetles (coleoptera): pheromones based on terpenoids, midges (a group of flies; diptera): pheromones based on diacetoxy alkanes, pentatomides (a group of bugs; heteroptera): pheromones based on alkene esters. At the moment, these pheromones are not well known from a regulatory point of view. However, the REBECA project assumes that many of these pheromones have similar safety profiles as the SCLPs, and suggests relaxed registration requirements, as soon as this assumption is confirmed (see above).

The REBECA proposals imply the following approach to overcome these knowledge gaps:

1. At the moment, non-lepidopteran pheromones have to be evaluated on a case-by-case basis.
2. With increasing experience (i.e. when ca 3 – 5 products for one taxonomic group have been registered), a more generic regulatory approach should be taken, comparable to that suggested above for SCLPs.
3. In this case, the issue of data protection needs to be resolved.

In the semiochemicals workshop during the REBECA Final Conference, it was mentioned that some prescribed study designs are inappropriate for SCLPs. Risk rather than hazard should be emphasized (i.e. should be the deciding factor). This should be discussed with the classification and labelling group.

Annex: letter from IBMA dated 3 August 2007

**IBMA proposals for REBECA
concerning Biochemical Substances (including Botanicals)**

Document issued on 3rd August 2007

On 22nd May 2007 IBMA held an internal meeting in Basle to discuss regulatory issues related to natural products. The present document summarises the key issues discussed in the meeting, statements and remarks made in common by the attendees for submission to the REBECA Project.

1) Reproducibility of production processes for natural products

The group recognises that the reproducibility of the production process for a botanical or other biochemical is essential. It must allow to obtain a product of constant quality which matches established specifications. All production parameters known to have a significant impact on the quality of the product should be described.

2) Natural products: can it be justified to take them out of the scope of European PPP directive/regulation?

The group tried to identify specific characteristics of natural products which might justify their specific status and treatment in the evaluation and authorisation process. It is possible to distinguish natural products by their origin:

- Botanicals (e.g. plant extracts)
- Minerals or inorganic matter (e.g. kaolin, clay, diatomaceous earth / amorphous silica, rock powder)
- Substances or products of animal origin (e.g. milk extract or derivatives, propolis)
- Substances or products produced by micro-organisms.

All natural products are present in nature and thus there is a potential exposure to them.

Typically natural products are biodegradable and thus they are less persistent and leave less residues but this does not apply to all of them, especially mineral products may be very persistent

Frequently natural products have a complex composition and contain more than one biologically active substance but this is not true for all of them.

Typically they have low human tox but there are relevant exceptions for acute tox (e.g. nicotine, alkaloids, glycosides), long term tox and CMR (Carcinogenicity, mutagenicity and reprotox).

Frequently natural compounds have a low impact on non-target organisms but some have a high impact (e.g. fish tox of rotenone).

In fact for each general feature or characteristic of natural products (and even botanicals) it is possible to find examples which do not match and at the same time some chemical compounds show at least some of the positive general features of natural products.

Some natural product have a pest specific mode of action but others don't (e.g. pyrethrum extract has a large spectrum of activity, avermectins are large spectrum insecticides and nematicides)

Thus the IBMA group on natural products concluded that it was not possible to maintain general claims for all natural products which are a heterogeneous group. However it choose to adopt a definition based on the mode of action which applies to a larger group of natural products, which can be called “**Biochemical substances**” and is defined as follows:

- (1) *Is a naturally-occurring substance or structurally-similar and functionally identical to a naturally-occurring substance;*
- (2) *Has a history of exposure to humans and the environment demonstrating minimal toxicity, or in the case of a synthetically-derived biochemical substance, is equivalent to a naturally-occurring substance that has such a history; and*
- (3) *Has a non-toxic mode of action to the target pest(s).*

This definition would cover (but not be limited to):

- natural plant regulators and products stimulating the natural defences of plants inducing plant resistance against pests and pathogens
- natural insect regulators e.g. insect juvenile growth hormones
- enzymes (e.g. extracted from milk)
- edible vegetable oils even when acting by suffocation must also be included
- semiochemicals (e.g. insect pheromones but also insect attractants or repellents released by plants)

Inorganic products e.g. kaolin, clay and diatomaceous earth could be assimilated on a case by case basis since their mode of action is based on mechanical action and /or dessiccation.

The group suggests that mineral and paraffin oils not be included in the scope of the above definition.

With regard to the status of Biochemical Substances under the PPP-directive, the IBMA group made the following statement:

IBMA wishes a specific approach to Biochemical Substances which might be given by a separate specific regulation for biocontrol products. However, in the mean time, under the current directive and regulations, the association supports the use of specific guidance documents covering procedures and requirements.

3) SANCO Draft Working Document 10472/2003 concerning data requirements for active substances of PPP made from plants or plant extracts (10472/2003, 6 July 2004):

Is the extension to other processes and products possible ?

It is desirable that the document has a larger scope or that similar guidance documents be developed for Biochemical Substances.

4) Minutes of the meeting of the Rebeca Botanicals Working Group in Salzau (20-21/09/2006) :
discussion of key points

On 1st June Dr Bernhard Speiser/FiBL/Switzerland circulated a new draft document with a “REBECA proposal on facilitations in the registration requirements for botanicals” but at the time of the IBMA meeting on 22nd May this was not yet available and thus the minutes of the Rebeca WG Botanical which took place in Salzau on 21st and 22nd Sept. 2006 were the basis of the discussion.

Item 1 (Strategies to implement the results of the working group):

It is acknowledged that the European Commission has more flexibility to draft and implement guidance documents (which still require acceptance by the Member States) than to develop a new regulation but IBMA requests a regulation that is flexible enough for a specific approach to Biochemical Substances.

Item 2 (Definition of «botanicals»):

The scope of the next Rebeca Workshop on Botanicals should be extended to other Biochemical Substances.

Item 3 (Characterization of «substance»):

Directive 91/414/EEC demands in annex I part A under point 1.10:

Identity of isomers, impurities and additives (e.g. stabilisers), together with the structural formula and the content expressed as g/kg

[...]

For each component, present in quantities of 1 g/kg or more, the following information, where relevant, must be provided:

- *chemical name according to IUPAC and CA nomenclature,*
- *ISO common name or proposed common name if available,*
- *CAS number, EEC (EINECS or ELINCS) number, and CIPAC number if available,*
- *molecular and structural formula,*
- *molecular mass, and*
- *maximum content in g/kg.*

IBMA supports the recommendations made by the WG in Salzau with regard to the characterisation: *more flexibility is required* when identifying and quantifying substances in botanicals and other “Biochemicals”. The characterisation should be made according to the current state-of-the art level of analytical techniques. The threshold of 1 g/ kg mentioned in the directive should not be applied systematically to all compounds of botanicals or other Biochemicals. Toxicological relevance should determine analytical requirements i.e. concentration limits for identification and precise quantification. The presence of similar or the same compounds in edible plant parts or plants at comparable concentrations should be taken into account as well when fixing limits for precise quantification.

Item 4 (Guidance document ,botanicals‘ SANCO/10472):

Biochemicals are not always plant extracts and a larger approach than in the SANCO draft document concerning data requirements for act. substances and PPP 10474/2003 made from plants or plant extracts is necessary.

Item 5 (Plant strengtheners [Sanco/1003/2000 rev.3]:

Natural Plant strengtheners fall under the definition of and thus should be treated as part of the Biochemical Substances group and like those should benefit from a specific harmonised approach in all E.U. Member States.

Item 6 (Interaction of registration between PPP and Biocides):

Biocides products directive and related regulations should provide for a specific approach for Biochemical Substances as well. Requirements for the should be harmonised with those for PPP wherever possible.

Item 7 (Risk assessment / waivers):

IBMA asks for a harmonised approach to waivers in all E.U. Member States.

Item 8 (Mode of action):

Salzau WG recommendations: (i) Botanicals are defined by origin and not by mode of action (ii) case-by-case consideration needed independent of mode of action since plant extracts consist of multiple compounds.

IBMA supports the definition of Biochemical Substances which is not based on origin (from plants) alone but takes also into consideration the non lethal mode of action for the pest and the history of exposure. An approach exclusively based on the origin whether natural or botanical does not address concerns about the safety of products. It is recognised that the mode of extraction/production can contribute to the selection of compounds with different safety profiles.

Item 9 (Formulation):

IBMA recommends the use of environmentally friendly and low toxicity co-formulants but at present the association has not defined any principles for co-formulants.

Item 10 (Proposals for research programmes):

No subjects for projects / research programmes related to Biochemical Substances which would require funding in the near future have been identified so far.

5) Approach to waivers

Writing justifications for non submission of data (= waivers) may be very time consuming and even expensive when outsourced.

There is also a risk that waivers may not be accepted and in that case it might become necessary to conduct studies to generate data to complete or replace the argumentation.

In some cases it might be faster to perform studies rather than writing argumentation.

These statements highlight typical difficulties related to waivers as experienced under the current European regulations.

Thus it seems desirable that applicants have access to typical waivers which are acceptable to regulators. In the following discussion in the group it was recognised that companies which have invested time and money to develop waivers and taken the risk see them rejected may not be willing to share their argumentation and might even wish to protect their waivers.

The group has identified the following options to prepare waivers or to compile them in guidance documents:

- Regulatory authorities may give examples in guidance documents
- Industry may for Task forces or even larger project groups could be formed involving other stakeholders to waivers of common interest for groups of compounds which might be shared collectively
- Applicants (or working groups) might get access to waivers published by US EPA (e.g. the outstanding part of the OECD working document currently in the BPSG)
- Waivers could be developed on the basis of the EU DARS or Final Monographs which are published
- IBMA member companies might be willing to share their experience with waivers and might circulate the monographs of their substances

IBMA wants to stress that a specific regulation with a tiered approach for biocontrol products including a section for biochemical substances would reduce the number of waivers required.

6) Need to establish biological efficacy (agronomic benefit)

When discussing general IBMA policy the group acknowledged that the efficacy of a Biochemical Substance should be demonstrated prior to its authorisation. However in this context efficacy should correspond to at least one agronomic benefit.

Reduced requirements and reduced numbers of trials must be accepted for biochemical products generally used in niche markets.