Opinion of the Scientific Committee on Plants on Endocrine disruption relevance in the context of Council Directive 91/414/EEC concerning the placing of plant protection products on the market (Opinion expressed by the Scientific Committee on Plants on 2 December 1999)

TERMS OF REFERENCE

The SCP had identified endocrine disruption (ED) at its third plenary meeting (9-10 February 1998) as a subject of potential interest for its work on plant protection products (PPP). However, the Committee decided at that time to defer further consideration of the topic until the Scientific Committee on Toxicology, Ecology and the Environment (CSTEE) had finalised its opinion on ED with respect to chemicals in general. The Committee appointed a small working group (M. Maroni and H. Kuiper) to keep the Committee informed of developments in the area. Following the adoption by the CSTEE of its opinion, the SCP decided to resume its examination of the possible implications of ED for plant protection products in the context of Directive 91/414/EEC. The Committee identified the following aspects, which it would address in its opinion:

1. The possible relevance of ED for the assessment of chemical PPP carried out under Directive 91/414/EEC;

2. The possible need for supplementary testing procedures beyond those provided for in Annex 2 to Directive 91/414/EEC.

OPINION OF THE SCP

1. The term Endocrine Disruption (ED) denotes the ability of exogenous chemicals to alter function(s) of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub) populations. Extensive information has become available on ED in recent years (1-4) and this subject has also been recently reviewed and discussed by the CSTEE for its relevance to the assessment of the impact of chemical substances on man and environment (5).

2. With respect to the assessment of PPPs carried out under Directive 91/414/EEC, the SCP notes that this group of chemicals shows remarkable differences when compared to other chemical substances, as PPP active substances are extensively investigated from the toxicological point of view and comprehensive dossiers are made available to support their registration. The contents of such dossiers are determined by Annex 2 of the Directive 91/414/EEC and provide for a wide range of animal tests including, among the others, acute and repeated dose toxicity studies, metabolic studies, mutagenicity studies, carcinogenicity studies, reproductive toxicity studies, and neurotoxicity studies. Thus the toxicological properties of the active substances of PPP on mammalians are generally well characterised for any possible effect, including those that may be caused by an endocrine disruption mechanism. Also with regard to ecotoxicology, the database for PPPs is clearly more favourable than that for other chemicals. Annex 2 of Directive 91/414/EEC requires long-term tests which regularly encompass reproductive end points for birds and aquatic invertebrates if

continued or repeated exposure of these organisms may occur; equivalent fish tests are also listed in certain circumstances. These ecotoxicological tests are the most advanced tests currently available with validated and internationally-harmonised protocols, but nevertheless they are not fully satisfactory when endocrine disrupting chemicals are in question.

3. To support the view that the current scheme of assessment of PPP enables the identification of endocrine-related effects, the SCP notes that several PPP active substances have shown toxic effects resulting from interference with the endocrine system, and such effects have been identified within the frame of the current practice of toxicological assessment carried out under the provisions of Annex 2 of Directive 91/414/EEC. Examples of endocrine disrupters so far evaluated by SCP are represented by fenarimol, vinclozolin, and isoxaflutole, each of which possesses a different mechanism of action. Therefore the SCP believes that the information currently provided for in the toxicological assessment of active substances enables the identification of ED-related effects in mammalians, provided that due attention is paid in the evaluation process to those elements which may alert assessors to the presence of an ED-related mechanism of action or outcome.

4. The situation is less favourable for ecotoxicological effects. To allow a proper risk assessment, the test programme should ideally reveal all ecotoxicological relevant effects of the test substance, such as, reproductive impairment and lowered survival rate including the dose-response characteristics. The details of the mechanism are only of secondary importance and this also holds for ED-related mechanisms. However these typically affect certain phases in the reproductive cycle, so potential effects may remain undetected if a test covers only a part of the reproductive cycle, as it is the case in the avian one-generation study or the fish early-life-stage test. Deficiencies in the current assessment scheme are especially related to the testing of aquatic and terrestrial invertebrates, but unfortunately, due to gaps in basic knowledge and the large variety of endocrine systems in invertebrates, international experts are far from being able to recommend suitable standard tests for regulatory purposes.

5. While expressing the above judgements, the SCP is aware that the set of toxicological tests required under the provisions of the Annex 2 of the Directive 91/414/EEC, was developed at a time when scientific knowledge about ED was rather limited and this sometimes resulted in a lack of specificity for certain of the tests to address ED-related mechanisms as well as biological and toxicological indicators. This fact is noteworthy for the current recommended guidelines for the conduct of the mammalian tests, which in some cases do not include the measurement of specific endocrine-related parameters such as hormone plasma levels, hormone-regulating factors, hormonal receptor binding etc. Therefore SCP is of the opinion that the current guidelines for toxicological testing could be improved with the aim of increasing sensitivity and specificity of detection of ED-related effects.

6. The desirability of improved toxicological testing methods for ED-related effects of chemicals, is widely acknowledged in the scientific community and has been matter of intense debate over the past two to three years in various agencies and international fora. The Organisation for Economic Co-operation and Development (OECD), as an international body engaged in scientific policy harmonisation throughout the world, has initiated a programme to develop new, and revise the existing, test guidelines, relevant to this subject. There is particular focus on the existing guideline 407 for the repeated oral toxicity test in rodents, the existing guideline 416 for the two-generation reproduction toxicity test, and guideline 206 for the avian reproduction test. The process of revising these existing guidelines is expected to be concluded in 2 or 3 years and will lead to the availability of improved, more comprehensive

testing methods which will likely be adopted by all regulatory agencies. The SCP is of the opinion that it is necessary to wait for the result of the OECD programme before recommending to the European Commission to change the existing testing protocols and consequently introduce amendments to the Annex 2 of the Directive 91/414/EEC. Also in the area of development of new test guidelines, OECD has started the work and at present Working Groups are dealing with new tests such as for example fish studies and new avian reproductive studies. Thus, with regards to both toxicological and ecotoxicological tests, the SCP recommends waiting for the results of the OECD programme before amending Annex 2 of the Directive 91/414/EEC.

7. The SCP stresses that ED has to be viewed as one of the many existing modes of action of chemicals in their interaction with the living organisms. As such, a better appreciation of this mechanism will not change the conceptual frame-work under which risk assessment is currently done. Actually already with the existing testing schemes provided for by Annex 2 of the Directive 91/414/EEC, endocrine effects are taken into consideration when they ultimately produce toxic effects. The SCP recommends to the risk assessors of the EC and the member states that in the evaluation of the dossiers of the active substances of PPP due attention be paid to a number of effects that, when present, may indicate an underlying endocrine mechanism of action. Such alerting outcomes include major endocrine organ changes or abnormalities in the acute and chronic toxicological studies, the presence of tumours in endocrine organs (mammary tumours, ovarian and testicular tumours, thyroid tumours, adrenal tumours), evidence of reproductive effects affecting fertility, neurological development, sex differentiation, sex organ maturation, mating behaviour changes etc. In the presence of such alerting outcomes, particularly when they represent the critical effect in term of dose, it is recommended that a peer examination be made in order to ascertain the possible origin of such effects and, whenever appropriate, further specific studies be requested for a complete elucidation of the phenomenon. Such a proactive approach would offer the best possibility of not overlooking relevant endocrine effects when using the current risk assessment process. In the case of the ecotoxicological area, the SCP recommends that the evaluation of PPPs for the time being should follow a flexible approach. Assessors should make use of the mammalian toxicology package which not only is valuable to assess the risk for wild mammals, but also indicates endocrine mechanisms for vertebrates in general much better than any screening method. In the case of alerting results, special attention should be paid to the toxicological assessment and further test be required if necessary.

The SCP recommends that risk assessors devote special attention to ED-related outcomes when examining PPP active substances for which the toxicological studies were generated before scientific knowledge and the wider implications of ED were recognised.

CONCLUSIONS

1. The SCP is following the scientific progress in the knowledge about ED with attention, but does not consider this problem to be of great concern for the assessment of PPP currently carried out under Directive 91/414/EEC because the current process of evaluation, if conducted with specific attention to this issue, already permits a rather comprehensive appreciation of the ED-related toxicological risk for mammalians and man. Also ecotoxicological risks arising from ED generally can be captured by the current assessment scheme, although for some species (in particular invertebrates) the test programme is not yet satisfactory.

2. While a further refinement of the protocols in use for the toxicological testing of the active substances of PPP as provided for by the Annex 2 of the Directive 91/414/EEC is deemed to be desirable by SCP in the near future, the SCP considers it appropriate to wait for the conclusion of the ongoing ED test guideline-update and development programme by OECD before recommending to the EU to undertake specific actions aimed at introducing supplementary testing in the Annex 2 of the Directive 91/414/EEC.

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