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COMMISSION DIRECTIVE 94/79/EC

of 21 December 1994

amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market

(OJ L 354, 31.12.1994, p. 16)

Corrected by:

►**C1** Corrigendum, OJ L 280, 23.11.1995, p. 58 (94/79/EC)

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COMMISSION DIRECTIVE 94/79/EC

of 21 December 1994

amending Council Directive 91/414/EEC concerning the placing of plant protection products on the market

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market [1], as last amended by Directive 94/43/EC [2], and in particular Article 18 (2) thereof,

Whereas Annexes II and III to Directive 91/414/EEC set out the requirements for the dossier to be submitted by applicants respectively for the inclusion of an active substance in Annex I and for the authorization of a plant protection product;

Whereas it is necessary to indicate, in Annexes II and III, to the applicants, as precisely as possible, any details on the required information, such as the circumstances, conditions and technical protocols under which certain data have to be generated; whereas these provisions should be introduced as soon as available in order to permit applicants to use them in the preparation of their files;

Whereas it is now possible to introduce more precision with regard to the data requirements concerning toxicological and metabolism studies on the active substance provided for in Section 5 of Part A of Annex II;

Whereas it is also now possible to introduce more precision with regard to the data requirements concerning toxicological studies on the plant protection product provided for in Section 7 of Part A of Annex II;

Whereas the measures provided for in this Directive are in accordance with the opinion of the Standing Committee on Plant Health,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Directive 91/414/EEC is amended as follows:

1. in Part A of Annex II the section headed ‘5. Toxicological and metabolism studies on the active substance’ is replaced by Annex I hereto;
2. in Part A of Annex III the section headed ‘7. Toxicological studies’ is replaced by Annex II hereto;
3. Point 1.2 of the introduction to Annexes II and III is replaced by the following: ‘1.2 where relevant, be generated using test guidelines, according to the latest adopted version, referred to or described in this Annex; in the case of studies initiated before the entry into force of the modification of this Annex, the information shall be generated using suitable internationally or nationally validated test guidelines or, in the absence thereof, test guidelines accepted by the competent authority;’
4. in point 1.3 of the introduction to Annexes II and III, the following words are added at the end: ‘in particular, when reference is made in this Annex to an EEC Method which consists in the transposal of a method developed by an international organization (e.g. OECD), Member States may accept that the required information is generated according to the latest version of that method if at the initiation of the studies the EEC Method has not yet been updated;’.

[1] OJ No L 230, 19. 8. 1991, p. 1.
[2] OJ No L 227, 1. 9. 1994, p. 31.

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Article 2

Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 31 January 1996. They shall immediately inform the Commission thereof.

When Member States adopt these provisions, these shall contain a reference to this Directive or shall be accompanied by such reference at the time of their official publication. The procedure for such reference shall be adopted by Member States

Article 3

This Directive shall enter into force on 1 February 1995.

Article 4

This Directive is addressed to the Member States.

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ANNEX I

‘5. TOXICOLOGICAL AND METABOLISM STUDIES

Introduction

(i) The information provided, taken together with that provided for one or more preparations containing the active substance, must be sufficient to permit an evaluation to be made as to the risks for man, associated with the handling and use of plant protection products containing the active substance, and the risk for man arising from residual traces remaining in food and water. In addition, the information provided must be sufficient to:

— permit a decision to be made as to whether, or not, the active substance can be included in Annex I,

— specify appropriate conditions or restrictions to be associated with any inclusion in Annex I,

— classify the active substance as to hazard,

— establish a relevant acceptable daily intake (ADI) level for man,

— establish acceptable operator exposure level(s) (AOEL),

— specify the hazard symbols, the indications of danger, and the risk and safety phrases for the protection of man, animals and the environment to be included in packaging (containers),

— identify relevant first aid measures as well as appropriate diagnostic and therapeutic measures to be followed in the event of poisoning in man, and

— permit an evaluation to be made as to the nature and extent of the risks for man, animals (species normally fed and kept or consumed by man) and of the risks for other non-target vertebrate species.

(ii) There is a need to investigate and report all potentially adverse effects found during routine toxicological investigations (including effects on organs and special systems such as immunotoxicity and neurotoxicity) and to undertake and report such additional studies which may be necessary to investigate the probable mechanism involved, to establish Noaels (no observed adverse effect levels), and to assess the significance of these effects. All available biological data and information which is relevant to the assessment of the toxicological profile of the substance tested, must be reported.

(iii) In the context of the influence that impurities can have on toxicological behaviour, it is essential that for each study submitted, a detailed description (specification) of the material used, as mentioned under section 1 point 11 be provided. Tests should be conducted using active substance of that specification to be used in the manufacture of preparations to be authorized, except where radiolabelled material is required or permitted.

(iv) Where studies are conducted using an active substance produced in the laboratory or in a pilot plant production system, the studies must be repeated using the active substance as manufactured, unless it can be justified that the test material used is essentially the same, for the purposes of toxicological testing and assessment. In cases of uncertainty, appropriate bridging studies must be submitted to serve as a basis for a decision as to the possible need for repetition of the studies.

(v) In the case of studies in which dosing extends over a period, dosing should preferably be done using a single batch of active substance if stability permits.

(vi) For all studies actual achieved dose in mg/kg body weight, as well as in other convenient units, must be reported. Where dosing via the diet is utilized the test compound must be distributed uniformly in the diet.

(vii) Where, as a result of metabolism or other processes in or on treated plants, or as a result of processing of treated products, the terminal residue (to which consumers or workers as defined in Annex III, point 7.2.3 will be exposed) contains a substance which is not the active substance itself and is not identified as a metabolite in mammals, it will be necessary to carry out toxicity studies on these components of the terminal residue unless it can be demonstrated that consumer or worker exposure to these substances does not constitute a relevant risk to health. Toxicokinetic and metabolism studies relating to metabolites and degradation products should

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only be conducted if toxicity findings of the metabolite cannot be evaluated by the available results relating to the active substance.

(viii) The way of administration of the test substance depends on the main exposure routes. In cases where exposure is mainly by the gas phase, it can be more appropriate to perform inhalation studies instead of oral studies.

5.1. **Studies on absorption, distribution, excretion and metabolism in mammals**

Quite limited data, as described below and restricted to one test species (normally the rat) may be all that is required in this area. These data can provide information useful in the design and interpretation of subsequent toxicity tests. However, it must be remembered that information on interspecies differences may be crucial in extrapolation of animal data to man and information on percutaneous penetration, absorption, distribution, excretion and metabolism may be useful in operator risk assessments. It is not possible to specify detailed data requirements in all areas, since the exact requirements will be dependant upon the results obtained for each particular test substance.

Aim of the test:

The tests should provide sufficient data to permit:

— an evaluation of the rate and extent of absorption,

— the tissue distribution and the rate and extent of excretion of the test substance and the relevant metabolites,

— the identification of metabolites and the metabolic pathway.

The effect of dose level on these parameters and whether results are different after single versus repeated doses, should also be investigated.

Circumstances in which required

A single dose toxicokinetic study in rats (oral route of administration) in at least two dose levels as well as a repeated dose toxicokinetic study in rats (oral route of administration) at a single dose level, must be conducted and reported. It may be necessary in some cases to perform additional studies on another species (such as goat or chicken).

Test guideline

Commission Directive 87/302/EEC of 18 November 1987 adapting to technical progress for the ninth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances [1], part B, Toxicokinetics.

5.2. **Acute toxicity**

The studies, data and information to be provided and evaluated must be sufficient to permit the identification of effects following a single exposure to the active substance, and in particular to establish, or indicate:

— the toxicity of the active substance;

— the time course and characteristics of the effects with full details of behavioural changes and possible gross pathological findings at post-mortem;

— where possible mode of toxic action; and

— the relative hazard associated with the different routes of exposure.

While the emphasis must be on estimating the toxicity ranges involved, the information generated must also permit the active substance to be classified in accordance with Council Directive 67/548/EEC. The information generated through acute toxicity testing is of particular value in assessing hazards likely to arise in accident situations.

5.2.1. *Oral*

Circumtances in which required

The acute oral toxicity of the active substance must always be reported.

Test guideline

The test must be carried out in accordance with the Annex to Commission Directive 92/69/EEC of 31 July 1992 adapting to technical progress

[1] OJ No L 133, 30. 5. 1988, p. 1.

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for the seventeenth time Council Directive 67/548/EEC on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances [1], Method B1 or B1 bis.

5.2.2. *Percutaneous*

Circumstances in which required

The acute percutaneous toxicity of the active substance must always be reported.

Test guideline

Both local and systemic effects must be investigated. The test must be carried out in accordance with Directive 92/69/EEC method B3.

5.2.3. *Inhalation*

Circumstances in which required

The inhalation toxicity of the active substance must be reported where the active substance is:

— a gas or liquified gas,

— is to be used as a fumigant,

— is to be included in a smoke generating, aerosol or vapour releasing preparation,

— is to be used with fogging equipment,

— has a vapour pressure > 1 × 10−2 Pa and is to be included in preparations to be used in enclosed spaces such as warehouses or glasshouses,

— is to be included in preparations which are powders containing a significant proportion of particles of diameter ►C1 < 50 μm ◄ (> 1 % on a weight basis), or

— is to be included in preparations to be applied in a manner which generates a significant proportion of particles or droplets of diameter < 50μm (> 1 % on a weight basis).

Test guideline

The test must be carried out in accordance with Directive 92/69/EEC Method B2.

5.2.4. *Skin irritation*

Aim of the test

The test will provide the potential of skin irritancy of the active substance including the potential reversibility of the effects observed.

Circumstances in which required

The skin irritancy of the active substance must be determined except where it is likely, as indicated in the test guideline, that severe skin effects may be produced or that effects can be excluded.

Test guideline

The acute skin irritation must be carried out in accordance with Directive 92/69/EEC Method B4.

5.2.5. *Eye irritation*

Aim of test

The test will provide the potential of eye irritancy of the active substance including the potential reversibility of the effects observed.

Circumstances in which required

Eye irritation tests must be conducted except where it is likely, as indicated in the test guideline, that severe effects on the eyes may be produced.

Test guidelines

The acute eye irritation must be determined in accordance with Directive 92/69/EEC Method B5.

[1] OJ No L 383A, 29. 12. 1992, p. 1.

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5.2.6. *Skin sensitization*

Aim of test

The test will provide sufficient information to assess the potential of the active substance to provoke skin sensitization reactions.

Circumstances in which required

The test must always be carried out except where the substance is a known sensitizer.

Test guideline

The test must be carried out in accordance with Directive 92/69/EEC Method B6.

5.3. **Short-term toxicity**

Short-term toxicity studies must be designed to provide information as to the amount of the active substance that can be tolerated without toxic effects under the conditions of the study. Such studies provide useful data on the risks for those handling and using preparations containing the active substance. In particular, short-term studies provide an essential insight into possible cumulative actions of the active substance and the risks to workers who may be intensively exposed. In addition short-term studies provide information useful in the design of chronic toxicity studies.

The studies, data and information to be provided and evaluated, must be sufficient to permit the identification of effects following repeated exposure to the active substance, and in particular to further establish, or indicate:

— the relationship between dose and adverse effects,

— toxicity of the active substance including where possible the Noael,

— target organs, where relevant,

— the time course and characteristics of poisoning with full details of behavioural changes and possible pathological findings at post-mortem,

— specific toxic effects and pathological changes produced,

— where relevant the persistence and reversibility of certain toxic effects observed, following discontinuation of dosing,

— where possible, the mode of toxic action, and

— the relative hazard associated with the different routes of exposure.

5.3.1. *Oral 28-day study*

Circumstances in which required

Although it is not mandatory to perform 28-day short term studies, they can be useful as range finding tests. Where conducted they must be reported, since the results could be of particular value in the identification of adaptive responses which can be masked in chronic toxicity studies.

Test guideline

The test must be carried out in accordance with Directive 92/69/EEC Method B7.

5.3.2. *Oral 90-day study*

Circumstances in which required

The short-term oral toxicity (90 day) of the active substance to both rat and dog, must always be reported. Where there is evidence that the dog is significantly more sensitive and where such data are likely to be of value in extrapolating results obtained to man, a 12-month toxicity study in dogs must be conducted and reported.

Test guidelines

Directive 87/302/EEC, Part B, sub-chronic oral toxicity test.

5.3.3. *Other routes*

Circumstances in which required

For the assessment of operator exposure additional percutaneous studies may be useful.

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For volatile substances (vapour pressure $>10^{-2}$ Pascal) expert judgment is required to decide whether the short term studies have to be performed by oral or inhalation exposure.

Test guidelines

— 28-day dermal: Directive 92/69/EEC Method B9,

— 90-day dermal: Directive 87/302/EEC, Part B, sub-chronic dermal toxicity study,

— 28-day inhalation: Directive 92/69/EEC Method B8,

— 90-day inhalation: Directive 87/302/EEC, Part B, sub-chronic inhalation toxicity study.

5.4. **Genotoxicity testing**

Aim of the test

These studies are of value in:

— the prediction of genotoxic potential

— the early identification of genotoxic carcinogens

— the elucidation of the mechanism of action of some carcinogens

To avoid responses that are artifacts of the test system, excessively toxic doses must not be used in either *in vitro* or *in vivo* assays for mutagenicity. This approach should be regarded as general guidance. It is important that a flexible approach is adopted, with selection of further tests being' dependant upon interpretation of results at each stage.

5.4.1. *In vitro studies*

Circumstances in which required

In vitro mutagenicity tests (bacterial assay for gene mutation, test for clastogenicity in mammalian cells and test for gene mutation in mammalian cells) must always be performed.

Test guidelines

Acceptable test guidelines are:

Directive 92/69/EEC Method B14 — *Salmonella Typhimurium* reverse mutation assay

Directive 92/69/EEC Method B10 — *in vitro* mammalian cytogenetic test

Directive 87/302/EEC, Part B — *in vitro* mammalian cell gene mutation test

5.4.2. *In vivo studies in somatic cells*

Circumstances in which required

If all the results of the *in vitro* studies are negative further resting must be done with consideration of other relevant information available (including toxicokinetic, toxicodynamic and physico-chemical data and data on analogous substances). The test can be an *in vivo* study or an *in vitro* study using a different metabolizing system from that/those previously used.

If the *in vitro* cytogenetic test is positive, an *in vivo* test using somatic cells (metaphase analysis in rodent bone marrow or micronucleus test in rodents) must be conducted.

If either of the *in vitro* gene mutation tests are positive, an *in vivo* test to investigate unscheduled DNA synthesis or a mouse spot test must be conducted.

Test guidelines

Acceptable test guidelines are:

Directive 92/69/EEC Method B12 — Micronucleus test,

Directive 87/302/EEC Part B — Mouse spot test,

Directive 92/69/EEC Method B11 — *In vivo* Mammalian Bone-Marrow cytogenetic test, Chromosomal analysis.

5.4.3. *In vivo studies in germ cells*

Circumstances in which required

When any result of an *in vivo* study in somatic cells is positive, *in vivo* testing for germ cell effects may be justified. The necessity for

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conducting these tests will have to be considered on a case by case basis, taking into account information regarding toxicokinetics, use and anticipated exposure. Suitable tests would need to examine interaction with DNA (such as the dominant lethal assay), to look at the potential for inherited effects and possibly make a quantitative assessment of heritable effects. It is recognized that in view of their complexity, the use of quantitative studies would require strong justification.

5.5. **Long term toxicity and carcinogenicity**

Aim of the test

The long-term studies conducted and reported, taken together with other relevant data and information on the active substance, must be sufficient to permit the identification of effects, following repeated exposure to the active substance, and in particular must be sufficient to:

— identify adverse effects resulting from exposure to the active substance,

— identify target organs, where relevant,

— establish the dose-response relationship,

— identify changes in toxic signs and manifestations observed, and

— establish the Noael.

Similarly, the carcinogenicity studies taken together with other relevant data and information on the active substance, must be sufficient to permit the hazards for humans, following repeated exposure to the active substance, to be assessed, and in particular must be sufficient:

— to identify carcinogenic effects resulting from exposure to the active substance,

— to establish the species and organ specificity of tumours induced,

— to establish the dose-response relationship, and

— for non-genotoxic carcinogens, to identify the maximum dose eliciting no adverse effect (threshold dose).

Circumstances in which required

The long-term toxicity and carcinogenicity of all active substances must be determined. If in exceptional circumstances, it is claimed that such testing is unnecessary, that claim must be fully justified, *viz.* toxicokinetic data demonstrates that absorption of the active substance does not occur from the gut, through the skin or via the pulmonary system.

Test conditions

A long-term oral toxicity and carcinogenicity study (two years) of the active substance must be conducted using the rat as test species; these studies can be combined.

A carcinogenicity study of the active substance must be conducted using the mouse as test species.

Where a non-genotoxic mechanism for carcinogenicity is suggested, a well argued case, supported with relevant experimental data, including that necessary to elucidate the possible mechanism involved, must be provided.

While the standard reference points for treatment responses are concurrent control data, historical control data, may be helpful in the interpretation of particular carcinogenicity studies. Where submitted, historical control data should be from the same species and strain, maintained under similar conditions and should be from contemporaneous studies. The information on historical control data provided must include:

— identification of species and strain, name of the supplier, and specific colony identification, if the supplier has more than one geographical location,

— name of the laboratory and the dates when the study was performed,

— description of the general conditions under which animals were maintained, including the type or brand of diet and, where possible, the amount consumed,

— approximate age, in days, of the control animals at the beginning of the study and at the time of killing or death,

— description of the control group mortality pattern observed during or at the end of the study, and other pertinent observations (e.g. diseases, infections),

— name of the laboratory and the examining scientists responsible for gathering and interpreting the pathological data from the study, and

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— a statement of the nature of the tumours that may have been combined to produce any of the incidence data.

The doses tested, including the highest dose tested, must be selected on the basis of the results of short-term testing and where available at the time of planning the studies concerned, on the basis of metabolism and toxicokinetic data. The highest dose level in the carcinogenicity study should elicit signs of minimal toxicity such as slight depression in body-weight gain (less than 10 %), without causing tissue necrosis or metabolic saturation and without substantially altering normal lifespan dueto effects other than tumours. If the long-term toxicity study is carried out separately, the highest dose level should elicit definite signs of toxicity without causing excessive lethality. Higher doses, causing excessive toxicity are not considered relevant to evaluations to be made.

In the collection of data and compilation of reports, incidence of benign and malignant tumours must not be combined, unless there is clear evidence of benign tumours becoming malignant with time. Similarly, dissimilar, un-associated tumours, whether benign or malignant, occurring in the same organ, must not be combined, for reporting purposes. In the interests of avoiding confusion, terminology such as that developed by American Society of Toxicologic Pathologists [1], or the Hannover Tumour Registry (RENI) should be used in the nomenclature and reporting of tumours. The system used must be identified.

It is essential that biological material selected for histopathological examination includes material selected to provide further information on lesions identified during gross pathological examination. Where relevant to the elucidation of mechanism of action and available, special histological (staining) techniques, histochemical techniques and electron microscopic examinations, must be conducted and reported.

Test guideline

The studies must be carried out in accordance with Directive 87/302/EEC, part B, Chronic toxicity test, Carcinogenicity test or combined chronic toxicity/carcinogenicity test.

5.6. **Reproductive toxicity**

Adverse reproductive effects are of two main types:

— impairment of male or female fertility, and

— impacts on the normal development of progeny (developmental toxicity).

Possible effects on all aspects of reproductive physiology in both males and females, as well as possible effects on pre-natal and post-natal development, must be investigated and reported. If in exceptional circumstances, it is claimed that such testing is unnecessary, that claim must be fully justified.

While the standard reference point for treatment responses are concurrent control data, historical control data may be helpful in the interpretation of particular reproductive studies. Where submitted, historical control data should be from the same species and strain, maintained under similar conditions and should be from contemporaneous studies. The information on historical control data provided must include:

— identification of species and strain, name of the supplier, and specific colony identification, if the supplier has more than one geographical location,

— name of the laboratory and the dates when the study was performed,

— description of the general conditions under which animals were maintained, including the type or brand of diet and, where possible, the amount consumed,

— approximate age, in days, of the control animals at the beginning of the study and at the time of killing or death,

— description of the control group mortality pattern observed during or at the end of the study, and other pertinent observations (e.g. diseases, infections), and

— name of the laboratory and the examining scientist responsible for gathering and interpreting the toxicological data from the study.

[1] *Standardized System of Nomenclature and Diagnostic Criteria — Guides for Toxicologic Pathology*

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5.6.1. *Multi-generation studies*

Aim of the test

The studies reported, taken together with other relevant data and information on the active substance, must be sufficient to permit the identification of effects for reproduction, following repeated exposure to the active substance, and in particular must be sufficient:

— to identify direct and indirect effects on reproduction resulting from exposure to the active substance,

— to identify any enhancement of general toxic effects (noted during short-term and chronic toxicity testing),

— to establish the dose-response relationship, to identify changes in toxic signs and manifestations observed, and

— to establish the Noael.

Circumstances in which required

A reproduction toxicity study in rats over at least two generations must always be reported.

Test guideline

The tests must be carried out in accordance with Directive 87/302/EEC, Part B, two-generation reproduction toxicity test. In addition organ weight of reproductive organs must be reported.

Supplementary studies

Where necessary for a better interpretation of the effects on reproduction and as far as this information is not yet available it could be necessary to perform supplementary studies in order to provide the following information:

— separate male and female studies,

— three segment designs,

— dominant lethal assay for male fertility,

— cross-matings of treated males with untreated females and vice versa,

— effects on spermatogenesis,

— effects on oogenesis,

— sperm motility, mobility and morphology, and

— investigation of hormonal activity.

5.6.2. *Developmental toxicity studies*

Aim of the test

The studies reported, taken together with other relevant data and information on the active substance, must be sufficient to permit effects on embryonic and foetal development, following repeated exposure to the active substance, to be assessed, and in particular must be sufficient:

— to identify direct and indirect effects on embryonic and foetal development resulting from exposure to the active substance,

— to identify any maternal toxicity,

— to establish the relationship between observed responses and dose in both dam and offspring,

— to identify changes in toxic signs and manifestations observed, and

— to establish the Noael.

Furthermore, the tests will give additional information on any enhancement of general toxic effects of pregnant animals.

Circumstances in which required

The tests must always be carried out.

Test conditions

Developmental toxicity must be determined both to rat and rabbit by the oral route. Malformations and variations should be reported separately. A glossary of terminology and diagnostic principles for malformations and variations must be given in the report.

Test guideline

The tests must be carried out in accordance with Directive 87/302/EEC, Part B, teratogenicity test — rodent and non-rodent.

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5.7. **Delayed neurotoxicity studies**

Aim of the test

The test shall provide sufficient data to evaluate if the active substance could provoke delayed neurotoxicity after acute exposure.

Circumstances in which required

These studies have to be performed for substances of similar or related structures to those capable of inducing delayed neurotoxicity such as organophosphates.

Test guidelines

The test must be carried out in accordance with OECD Guideline 418.

5.8. **Other toxicological studies**

5.8.1. *Toxicity studies of metabolites as referred to in the introduction point (vii)*

Supplementary studies, where they relate to substances other than the active substance, are not a routine requirement.

Decisions as to the need for supplementary studies must be made on a case by case basis.

5.8.2. *Supplementary studies on the active substance*

In certain cases it can be necessary to carry out supplementary studies to further clarify observed effects. These studies could include:

— studies on absorption, distribution, excretion and metabolism,

— studies on the neurotoxic potential,

— studies on the immunotoxicological potential,

— studies on other routes of administration.

Decisions as to the need for supplementary studies must be made on a case by case basis, taking into account the results of the available toxicological and metabolism studies and the most important exposure routes.

Studies required must be designed on an individual basis, in the light of the particular parameters to be investigated and the objectives to be achieved.

5.9. **Medical data**

Where available, and without prejudice to the provisions of Article 5 of Council Directive 80/1107/EEC of 27 November 1980 on the protection of workers from the risks related to chemical, physical and biological agents at work [1], practical data and information relevant to the recognition of the symptoms of poisoning, and on the effectiveness of first aid and therapeutic measures have to be submitted. More specific references to the investigation for antidotal pharmacology or safety pharmacology using animals should be provided. Where relevant, the effectiveness of potential antagonists to poisoning, should be investigated and reported.

Data and information relevant to the effects of human exposure, where available and of the necessary quality, are of particular value, in confirming the validity of extrapolations made and conclusions reached with respect to target organs, dose-response relationships, and the reversibility of toxic effects. Such data can be generated following accidental or occupational exposure.

5.9.1. *Medicinal surveillance on manufacturing plant personnel*

Reports of occupational health surveillance programmes, supported with detailed information on the design of the programme, on exposure to the active substance and exposure to other chemicals, must be submitted. Such reports should, where feasible, include data relevant to the mechanism of action of the active substance. These reports shall, where available, include data from persons exposed in manufacturing plants or after application of the active substance (e.g.: in efficacy trials).

Available information on the sensitization including allergenic response of workers and others exposed to the active substance, must be provided, and include where relevant details of any incidence of hypersensitivity. The information provided should include details of frequency, level and

[1] OJ No L 327, 3. 12. 1980, p. 8.

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duration of exposure, symptoms observed and other relevant clinical information.

5.9.2. *Direct observation, e.g.: clinical cases and poisoning incidents*

Available reports from the open literature, relating to clinical cases and poisoning incidents, where they are from refereed journals or official reports, must be submitted together with reports of any follow-up studies undertaken. Such reports should contain complete descriptions of the nature, level and duration of exposure, as well as the clinical symptoms observed, first aid and therapeutic measures applied and measurements and observations made. Summary and abstract information is not of value.

Where supported with the necessary level of detail, such documentation can be of particular value in confirming the validity of extrapolations from animal data to man and in identifying unexpected adverse effects which are specific to humans.

5.9.3. *Observations on exposure of the general population and epidemiological studies if appropriate*

Where available, and supported with data on levels and duration of exposure, and conducted in accordance with recognized standards [1], epidemiological studies are of particular value and must be submitted.

5.9.4. *Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical tests*

A detailed description of the clinical signs and symptoms of poisoning, including the early signs and symptoms and full details of clinical tests useful for diagnostic purposes, where available, must be provided and include full details of the time courses involved relevant to the ingestion, dermal exposure or inhalation of varying amounts of the active substance.

5.9.5. *Proposed treatment: first aid measures, antidotes, medical treatment*

The first aid measures to be used in the event of poisoning (actual and suspected) and in the event of contamination of eyes must be provided.

Therapeutic regimes for use in the event of poisoning or contamination of eyes, including where available the use of antidotes, must be described in full. Information based on practical experience, where it exists and is available, in other cases on theoretical grounds, as to the effectiveness of alternative treatment regimes, where relevant, must be provided. Contraindications associated with particular regimes, particularly those relating to "general medical problems" and conditions, must be described.

5.9.6. *Expected effects of poisoning*

Where known, the expected effects and the duration of these effects following poisoning must be described and include the impact of:

— the type, level and duration of exposure, or ingestion, and

— varying time periods between exposure, or ingestion, and commencement of treatment.

5.10. **Summary of mammalian toxicity and overall evaluation**

A summary of all data and information provided under paragraphs 5.1 through 5.10, must be submitted, and include a detailed and critical assessment of those data in the context of relevant evaluative and decision making criteria and guidelines, with particular reference to the risks for man and animals that may or do arise, and the extent, quality and reliability of the data base.

Where relevant, in the light of findings with respect to the analytical profile of batches of the active substance (paragraph 1.11) and any bridging studies conducted (paragraphs 5 (iv)), the relevance of the data as submitted to the assessment of the toxicological profile of the active substance as manufactured, must be argued.

On the basis of an assessment of the data base, and the relevant decision making criteria and guidelines, justifications must be submitted for the Noaels proposed for each relevant study.

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[1] *Guidelines for Good Epidemiology Practices for Occupational and Environmental Research, developed by the Chemical Manufacturers Association's Epidemiology Task Group, as part of the Epidemiology Resource and Information Centre (ERIC),* Pilot Project, 1991

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On the basis of these data scientifically reasoned proposals for the establishment of ADI and AOEL(s) for the active substance must be submitted.’

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ANNEX II

‘7. TOXICOLOGICAL STUDIES

For proper evaluation of the toxicity of preparations sufficient information should be available on acute toxicity, irritation and sensitization of the active substance. If possible, additional information on mode of toxic action, toxicological profile and all other known toxicological aspects of the active substance should be submitted.

In the context of the influence that impurities and other components can have on toxicological behaviour, it is essential that for each study submitted, a detailed description (specification) of the material used, be provided. Tests must be conducted using the plant protection product to be authorized.

7.1. **Acute toxicity**

The studies, data and information to be provided and evaluated, must be sufficient to permit the identification of effects following a single exposure to the plant protection product, to be assessed, and in particular to establish, or indicate:

— the toxicity of the plant protection products,

— toxicity of the plant protection product relative to the active substance,

— the time course and characteristics of the effect with full details of behavioural changes and possible gross pathological findings at post-mortem,

— where possible the mode of toxic action, and

— the relative hazard associated with the different routes of exposure.

While the emphasis must be on estimating the toxicity ranges involved, the information generated must also permit the plant protection product to be classified in accordance with Council Directive 78/631/EEC. The information generated through acute toxicity testing is of particular value in assessing hazards likely to arise in accident situations.

7.1.1. *Oral*

Circumstances in which required

An acute oral test should always be carried out unless the applicant can justify to the satisfaction of the competent authority that Article 3.2 of Council Directive 78/631/EEC can be invoked.

Test guidelines

The test must be carried out in accordance with Directive 92/69/EEC Method B1 or B1 bis.

7.1.2. *Percutaneous*

Circumstances in which required

An acute percutaneous test should always be carried out unless the applicant can justify to the satisfaction of the competent authority that Article 3.2 of Council Directive 78/631/EEC can be invoked.

Test guideline

The test must be carried out in accordance with Directive 92/69/EEC Method B3.

7.1.3. *Inhalation*

Aim of the test

The test will provide the inhalation toxicity to rats of the plant protection product or of the smoke it generates.

Circumstances in which required

The test must be carried out where the plant protection product:

— is a gas or liquified gas,

— is a smoke generating formulation or fumigant,

— is used with fogging equipment,

— is a vapour releasing preparation,

— is an aerosol,

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— is a powder containing a significant proportion of particles of diameter <50 μm (> 1 % on a weight basis),

— is to be applied from aircraft in cases where inhalation exposure is relevant,

— contains an active substance with a vapour pressure > 1×10^{-2} Pa and is to be used in enclosed spaces such as warehouses or glasshouses,

— is to be applied in a manner which generates a significant proportion of particles or droplets of diameter <50 μm (> 1 % on a weight basis).

Test guideline

The test must be carried out in accordance with Directive 92/69/EEC Method B2.

7.1.4. *Skin irritation*

Aim of the test

The test will provide the potential of skin irritancy of the plant protection product including the potential reversibility of the effects observed.

Circumstances in which required

The skin irritancy of the plant protection product must be determined except where it is likely, as indicated in the test guideline, that severe skin effects may be produced or that effects can be excluded.

Test guideline

The test must be carried out in accordance with Directive 92/69/EEC Method B4.

7.1.5. *Eye irritation*

Aim of the test

The test will provide the protential for eye irritation of the plant protection product, including the potential reversibility of the effects observed.

Circumstances in which required

Eye irritation tests must be conducted except where it is likely, as indicated in the test guideline, that severe effects on the eyes may be produced.

Test guideline

The eye irritation must be determined in accordance with Directive 92/69/EEC Method B5.

7.1.6. *Skin sensitization*

Aim of the test

The test will provide sufficient information to assess the potential of the plant protection product to provoke skin sensitization reactions.

Circumstances in which required

The tests must always be carried out except where the active substance(s) or co-formulants are known to have sensitizing properties.

Test guideline

The tests have to be carried out in accordance with Directive 92/69/EEC Method B6.

7.1.7. *Supplementary studies for combinations of plant protection products*

Aim of the test

In certain cases it may be necessary to carry out the studies as referred to under points 7.1.1 to 7.1.6 for a combination of plant protection products where the product label includes requirements for use of the plant protection product with other plant protection products and/or with adjuvants as a tank mix. Decisions as to the need for supplementary studies must be made on a case by case basis, taking into account the results of the acute toxicity studies of the individual plant protection products, the possibility for exposure to the combination of the products concerned and available information or practical experience with the products concerned or similar products.

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7.2. **Data on exposure**

7.2.1. *Operator exposure*

The risks for those using plant protection products depend on the physical, chemical and toxicological properties of the plant protection product as well as the type of the product (undiluted/diluted), and on the route, the degree and duration of exposure. Sufficient information and data must be generated and reported to permit an assessment of the extent of exposure to the active substance(s) and/or toxicologically relevant compounds in the plant protection product likely to occur under the proposed conditions of use. It must also provide a basis for the selection of the appropriate protective measures including personal protective equipment to be used by operators and to be specified on the label.

7.2.1.1. Estimation of operator exposure

Aim of the estimation

An estimation shall be made, using where available a suitable calculation model, in order to permit an evaluation of the operator exposure likely to arise under the proposed conditions of use.

Circumstances in which required

An estimation of operator exposure must always be completed.

Estimation conditions

An estimation shall be made for each type of application method and application equipment proposed for use of the plant protection product taking account of the requirements resulting from the implementation of the classification and labelling provisions of Directive 78/631/EEC for handling the undiluted or diluted product as well as the different types and sizes of containers to be used, mixing, loading operations, application of the plant protection product, the climatic conditions and cleaning and routine maintenance of application equipment.

At first an estimation shall be made with the assumption that the operator is not using any personal protective equipment.

Where appropriate, a second estimation shall be made with the assumption that the operator is using effective and readily obtainable protective equipment which is feasible to be used by the operator. Where protective measures are specified on the label, the estimation will take these into account.

7.2.1.2. Measurement of operator exposure

Aim of the test

The test shall provide sufficient data to permit an evaluation of the operator exposure likely to arise under the proposed conditions of use.

Circumstances in which required

Actual exposure data for the relevant exposure route(s) must be reported where the risk assessment indicates that a health-based limit value is exceeded. This will, for example, be the case when the results of the estimation of operator exposure provided for under point 7.2.1.1 indicate that:

— the Acceptable Operator Exposure Level(s) (AOEL) established in the context of inclusion of the active substance(s) in Annex I, and/or

— the Limit Values established for the active substance and/or toxicologically relevant compound(s) of the plant protection product in accordance with Council Directive 80/1107/EEC and Council Directive 90/394/EEC of 28 June 1990 on the protection of workers from the risks related to exposure to carcinogens at work [1],

may be exceeded.

Actual exposure data must also be reported when no appropriate calculation model or no appropriate data are available to do the estimation provided for under point 7.2.1.1.

In cases where dermal exposure is the most important exposure route, a dermal absorption test or the results of a sub-acute dermal study, if not

[1] OJ No L 196, 26. 7. 1990, p. 1.

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already available, may be a useful alternative test to provide data in order to refine the estimate provided for under point 7.2.1.1.

Test conditions

The test must be done under realistic exposure conditions taking into account the proposed conditions of use.

7.2.2. *Bystander exposure*

Bystanders can be exposed during the application of plant protection products. Sufficient information and data must be reported to provide a basis for the selection of appropriate conditions of use, including the exclusion of bystanders from treatment areas and separation distances.

Aim of the estimation

An estimation shall be made, using where available a suitable calculation model in order to permit an evaluation of the bystander exposure likely to arise under the proposed conditions of use.

Circumstances in which required

An estimation of bystander exposure must always be completed.

Estimation conditions

An estimation of bystander exposure must be made for each type of application method. The estimation shall be made with the assumption that bystanders do not use any personal protective equipment.

Measurement of bystander exposure may be required when estimates indicate a cause for concern.

7.2.3. *Worker exposure*

Workers can be exposed following application of plant protection products, when entering treated fields or premises or handling treated plants or plant products on which residues remain. Sufficient information and data must be reported to provide a basis for the selection of appropriate protective measures, including waiting and re-entry periods.

7.2.3.1. Estimation of worker exposure

Aim of the estimation

An estimation shall be made using where available a suitable calculation model, in order to permit an evaluation of the worker exposure likely to arise under the proposed conditions of use.

Circumstances in which required

The estimation of worker exposure must always be completed.

Estimation conditions

An estimation of worker exposure must be made for each crop and task to be carried out.

At first the estimation shall be made using available data on the exposure to be expected with the assumption that the worker is not using any personal protective equipment.

Where appropriate, a second estimation shall be made with the assumption that the worker is using effective and readily obtainable protective equipment which is feasible to be used.

Where appropriate, a further estimation shall be made using data generated on the amount of dislodgeable residues under the proposed conditions of use.

7.2.3.2. Measurement of worker exposure

Aim of the test

The test shall provide sufficient data to permit an evaluation of the worker exposure likely to arise under the proposed conditions of use.

Circumstances in which required

Actual exposure data for the relevant exposure route(s) must be reported where the risk assessment indicates that a health-based limit value is exceeded. This will, for example, be the case where the results

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of the estimation of worker exposure provided for under point 7.2.3.1 indicate that:

— the AOEL(s) established in the context of inclusion of the active substance(s) in Annex I,

and/or

— the Limit Values established for the active substance and/or toxicologically relevant compound(s) of the plant protection product in accordance with Council Directives 80/1107/EEC and 90/394/EEC,

may be exceeded.

Actual exposure data must also be reported when no appropriate calculation model or no appropriate data are available to do the estimation provided for under point 7.2.3.1.

Where dermal exposure is the most important exposure route, a dermal absorption test, if not already available, may be a useful alternative test to provide data in order to refine the estimate provided for under point 7.1.3.1.

Test conditions

The test must be done under realistic exposure conditions taking into account the proposed conditions of use.

7.3. **Dermal absorption**

Aim of the test

The test shall provide a measurement of the absorption of the active substance and toxicologically relevant compounds through the skin.

Circumstances in which required

The study must be conducted when dermal exposure is a significant exposure route and where the risk assessment indicates that a health-based limit value is exceeded. This will, for example, be the case where the results of the estimation or measurement of operator exposure provided for under points 7.2.1.1 or 7.2.1.2 indicate that:

— the AOEL(s) established in the context of inclusion of the active substance(s) in Annex I,

and/or

— the limit values established for the active substance and/or toxicologically relevant compound(s) of the plant protection product in accordance with Council Directives 80/1107/EEC and 90/394/EEC may be exceeded.

Test conditions

In principle data of an *in vivo* rat skin absorption study must be reported. If, when the results of the estimation using these *in vivo* skin absorption data are incorporated in the risk assessment, there remains an indication of excessive exposure, it may be necessary to perform an *in vivo* comparative absorption study on rat and human skin.

Test guideline

Appropriate elements of OECD guideline 417 are to be used. For the design of the studies it may be necessary to take into account the results of the skin absorption studies with the active substance(s).

7.4. **Available toxicological data relating to non-active substances**

Where available, a copy of the notification and the safety data sheet submitted in the context of Directive 67/548/EEC and Commission Directive 91/155/EEC of 5 March 1991 defining and laying down the detailed arrangements for the system of specific information relating to dangerous preparations in implementation of Article 10 of Council Directive 88/379/EEC [1] must be submitted for each formulant. All other available information should be submitted.'

[1] OJ No L 76, 22. 3. 1991, p. 35.