ANNEX II

REQUIREMENTS FOR THE DOSSIER TO BE SUBMITTED FOR THE INCLUSION OF AN ACTIVE SUBSTANCE IN ANNEX I

PART A

Chemical substances[(1)]

[F1 5. Toxicological and metabolism studies

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.

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.**]**

Textual Amendments

F1 Substituted by 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.

(**1**) Substance within the meaning of the definition of Article 2, point 3.