

REFINED WAIVING CONCEPT FOR RODENTICIDES

Addendum to the TNsG on Data Requirements,

Chapter 1.4 (Guidance on non-submission of data)

1.4.1 Specific considerations for some product types.

PT14 RODENTICIDES

This document was endorsed at the 15th meeting of representatives of Members States Competent Authorities for the implementation of Directive 98/8/EC concerning the placing of biocidal products on the market (15-16 December 2003).

Without prejudice to Articles 5(2) and 10(1) of Directive 98/8/EC, waiving of certain toxicological studies on rodenticidal active substances could be possible, if the prerequisites on both human exposure and toxicological profile, as generally outlined in the TNsG on data requirements chapter 1.4, are satisfied. The following text details the waiving issues for PT14, rodenticides.

The necessary data and the justification for waiving should be submitted to the Rapporteur Member State for a specific active substance. Waiving of certain studies should be a **case-by-case** decision for each specific active substance in a relevant product type.

Waiving is only possible before the initiation of a study. If a study on vertebrate animals is already on-going, aspects concerning both ethical and economical reasons must be considered. Therefore, waiving of an already initiated study is not supported.

The Directive 98/8/EC states in Article 8 (5) that "... a justification, acceptable to the Competent Authority must be submitted...". On the other hand, it should be common practice under the Review Regulations that the competent authority should provide a reasoned statement for not accepting or accepting such a justification for waiving of certain toxicological studies. Such statements should be discussed between the different Member States (or in the Waiving Working Group) and based on the outcome of a waiving decision, it is possible, if applicable in general, that the decision is reflected in the "Manual of Decisions". It is the opinion of the Waiving Working Group that arguments and decisions in relation to waiving of studies in a specific case should be transparent.

A detailed waiving concept is given in the TNsG on data requirements. This waiving concept is, in general, also applicable to rodenticidal active substances especially with regard to the toxicological core-data studies. A refinement of this waiving concept was required for Product Type 14. The following toxicological data requirements from the common core data set may be considered for the application of the waiving principles for rodenticidal active substances:

- Subchronic toxicity study (90-days) in rodents
- Chronic toxicity studies in rodents
- Carcinogenicity studies in rodents
- Teratogenicity study in the second species (normally in rats)
- Two-generation reproduction (fertility) toxicity study

1. General considerations for waiving of several toxicity studies on rodenticides

Some general considerations for non-submission of data or toxicological studies from the common core data set are outlined below.

1. The study is technically not possible to perform

- The intrinsic physico-chemical or other (e.g. toxicological) properties of the rodenticidal active substances are such that specific route of exposure cannot be tested or not all tests can be performed (e.g. very volatile or unstable substances (CO₂, Phosphides) by oral application or cannot be tested particularly in long-term studies).

2. Other existing data can be used instead of the required data:

- Active substances evaluated with regard to the agricultural use
 - For the majority of rodenticides there are many toxicological data available and these have been evaluated with regard to agricultural use. These data (amended with biocidal use specific considerations) might generally be sufficient also for the evaluation as biocidal active substance under Directive 98/8/EC.
 - The waiving principles discussed for a specific active substance under Directive 91/414/EEC should be considered and as far as possible used for the assessment under Directive 98/8/EC, especially if comparable exposure scenarios are applicable.
- Bridging/Read-across concept for data on related substances
 - A toxicological study can be waived, if a bridging/read-across concept for two closely related chemical substances (e.g. isomers) can be applied under the conditions that
 - sufficient relevant core data (including physical-chemical and toxicological data) are available for both active substances. Mechanistic studies may be needed to clarify the mode of action of substance(s). All these data should lead to the scientifically based conclusion that both substances have the same toxicological profile.
 - In such cases, it is possible to waive specified investigations with the second substance, especially for testing of long term toxicity/carcinogenicity and reproduction toxicity, if the data obtained for the first substance allow a valid assessment of the toxicological properties of the second substance and vice-versa.
- Evaluation of acceptable human data
 - Although most data required for human health risk assessment will be obtained from animal studies, the evaluation of acceptable and ethically derived human data is important since it can supplement findings in animal studies.
 - Such data may include information following medical use (e.g. Warfarin), accidental or occupational exposure, and medical surveillance data on manufacturing plant personnel.
 - Such data on rodenticidal active substances must not include information coming from human volunteer studies.

3. The study is not scientifically necessary

- In some cases it is not scientifically advisable to perform a toxicological study due to the intrinsic properties of the chemical. For example, the tests using rats as test animals may not suit several rodenticides. Therefore, a modification of the test guideline might be needed, particularly with regard to the *choice of species*. However, the choice of species must be justified by the applicant.
- In the case of rodenticides, designed to kill the wild form of the recommended test species, reproduction or long-term testing of the target species may be inherently difficult. Where alternative test species are more suitable for toxicity testing, derogation from the data requirements laid down in the TNsG on Data Requirements may be appropriate.
- Owing to the activity of the rodenticide where, in consequence, the tests using rats as the preferred test animals may not be suitable another species (i.e. mice or hamsters instead of rats for rodenticides with selective high efficacy to rats) might be considered for the toxicological testing according to the common core data set.
- If, for any endpoint of the common core data set, testing on two species is required, i.e. tests in rodents and non-rodents, the rodent species (e.g. rats) might be considered as “second species” for rodenticides and non-rodents should be used as the first species, if a lower sensitivity can be assumed.

4. The study is not necessary due to limited exposure and toxicity profile

- Primary exposure (including occupational exposure during mixing and loading) and secondary exposure (including possible contamination of food or feed) must be estimated according to validated exposure models based on a realistic worst case exposure scenarios.
- Primary exposure to rodenticides is mostly limited to the formulating personnel and pest control operators (including amateur use, where this is still permitted).
- The predominant use of rodenticides is protected (e.g. bait stations, enclosed boxes designed to be ‘tamper-proof’), such that members of the general public can only gain access to the baits with the use of force. This minimises the chances of secondary exposure, which might be considered as NEGLIGIBLE (including no residues in food or feed), if demonstrated by realistic worst case exposure scenarios.
- The possibility of accidental or suicidal exposure to the public should be considered in the risk assessment as a consequence of an inappropriate use.
- If data is adequate to indicate any health risks in humans and non-rodent animals, waiving of the following data requirements from the common core data set may be considered, in particular if specific exposure and use conditions will be linked to the Annex I listing of the active substance.
- In addition, the experimental test data available for each active substance must be sufficient to identify any direct and indirect effects regarding all endpoints covered by the studies below.

The following criteria may be applicable when a reasoned statement has been presented demonstrating that the rodent species are of less relevance for the human risk assessment.

- Subchronic toxicity study (90-days) in the second animal species for rodenticides

Exposure:

- if the level of secondary exposure to the rodenticidal active substances is NEGLIGIBLE.

Toxicity profile:

- if the repeated-dose studies in the first species, preferably performed in agreement with the OECD test guidelines on non-rodents, are without indication of substance-related adverse effects for primary exposure (including a satisfactory MOE¹), **and**
- if the mechanism of the toxicity is known and it is justified that the toxicological effects in the target rodent species are not relevant to humans regarding the expected exposure levels².

- Chronic toxicity studies in rodents

Exposure:

- if the level of secondary exposure is NEGLIGIBLE, **and**
- if the frequency or duration of the primary exposure to the rodenticidal active substance is below the level of lower concern with regard to long-term toxicity testing, i.e. up to once per month (may be average per year, i.e., up to 12 exposures per year) or a 3 month period, respectively.

Toxicity profile:

- if the sub-chronic repeated-dose studies performed in agreement with the OECD test guidelines are without indication of substance-related adverse effects for human exposure (including a satisfactory MOE¹), **and**
- if the mechanism of the toxicity is known and it is justified that the toxicological effects in the target rodent species are not relevant to humans regarding the expected exposure levels².

- Carcinogenicity studies in rodents

Exposure:

- if secondary exposure to the rodenticide is NEGLIGIBLE, **and**
- if the frequency or duration of the primary exposure to the rodenticidal active substance is below the level of lower concern with regard to long-term toxicity testing, i.e. up to once per month (may be average per year, i.e., up to 12 exposures per year) or a 3 month period, respectively.

Toxicity profile:

- if no genotoxic potential for humans is identified in tests of genotoxicity, performed in agreement with the OECD test guidelines (according to TNsG-DR chapter 2A, 6.6), **and**
- if possible mechanisms of toxic effects observed in subchronic and chronic toxicity studies are without any indications of non-genotoxic carcinogenicity and there are no structural alerts for carcinogenicity, **and**

¹ 300 to 1000 depending on the following considerations (see 4.1.3 Determining assessment factors in TNsG Annex I inclusion):

- the type and severity of the effect;
- possible differences in exposure characteristics between the calculated exposure and the exposure in the study providing the NOAEL
- the dose-response relationship observed;
- the overall confidence in the database (i.e. completeness of the database).

² based on a realistic worst-case scenario

- if the subchronic studies are without indication of substance-related adverse effects relevant to humans regarding the expected exposure levels².
- Teratogenicity study in the second animal species for rodenticides
Exposure:
 - if primary and secondary exposure², particularly of women in childbearing age, to the rodenticidal active substance is NEGLIGIBLE.Toxicity profile:
 - if no developmental or reproductive effects in the first teratogenicity study, performed in agreement with the OECD test guidelines, are observed in less susceptible species for a specific rodenticide (e.g. rabbits, mice, or hamsters), **and**
 - if no developmental or reproductive effects in the two-generation reproduction toxicity study (performed in agreement with the OECD test guidelines in a less susceptible species for a specific rodenticide, e.g. mice, hamster; and performed with another species than the first teratogenicity study) are observed.
- Two-generation reproduction (fertility) toxicity study
Exposure:
 - if primary exposure (including occupational exposure during mixing and loading) and secondary exposure², particularly to children (i.e. no residues in food or feed), to the rodenticidal active substance is NEGLIGIBLE.Toxicity profile:
 - if no developmental or reproductive effects are observed in the teratogenicity studies (performed in agreement with OECD guideline No 414) in two less susceptible species for a specific rodenticidal active substance (e.g. mice, hamster, rabbits), **and**
 - if the subchronic and chronic studies performed in agreement with the OECD test guidelines have shown no adverse effects on the reproductive organs (macroscopic investigation, organ weight analysis and histology) and endocrine functions, **and**
 - if the absence of effects on reproductive organs is not only investigated at a morphological level but also on their functionality and additional data on sperm quality and/or oestrus cycle to confirm no effect on functionality of the reproductive organs are sufficient. Where relevant for interpretation of such effects, it could be necessary to perform supplementary studies (e.g. as mechanistic in-vivo studies or as in-vitro studies according to established guidelines for testing of hormonal disrupters).

2. Considerations with regard to specific types of rodenticides

Anticoagulants (except Warfarin)

- A waiver for a multigeneration study and long-term rodent studies on anticoagulant rodenticides may be scientifically justified based on the above mentioned principles on a case-by case basis and supported by a sufficient database from animal studies and human observations.
- Support for waiving of one or more of these studies can come from the practical difficulties of performing a study in the target rodent species.

- Furthermore, exposure is an issue and has to be taken into account, e.g. a high ratio of the predicted dose in non-rodent studies and the actual dose of primary human exposure, and/or negligible levels of both long-term primary and long-term secondary exposure.

Warfarin

- Warfarin has been subject to a recent comprehensive discussion under directive 91/414/EEC. Although the available toxicological studies do not comply with current standards they can be used for risk assessment which is mainly based on human data, i.e., experience coming from the long-lasting medical use of this compound to avoid or reduce blood coagulation.
- New toxicological studies in animals are not required.
- In the framework of the evaluation of warfarin under directive 98/8/EC the list of endpoints, as established in the framework of 91/414/EEC shall be taken over, taking into consideration the rules on data protection and the list of protected data.

Carbon Dioxide (CO₂)

- The use of carbon dioxide as a rodenticide, under normal conditions of use, will not cause any detectable elevation in the level of carbon dioxide found naturally in air. Indeed, the volume of carbon dioxide in one trap, which gets released to atmosphere over 15 minutes, is equivalent to the amount released in an enclosed 25 m² room by one person breathing for six minutes.
- On the basis of exposure alone, it is not scientifically necessary to conduct a multi-generation study and/or a carcinogenicity study for carbon dioxide. The use of carbon dioxide as a rodenticide does not increase carbon dioxide above levels found naturally in the atmosphere, and this is well below established maximum occupational exposure limits for safe working conditions.
- A multi-generation and/or carcinogenicity study is technically feasible, but difficult, and given the body's metabolic and physiological sensitivity to changes in carbon dioxide levels it is unlikely to provide any useful data for the risk assessment.
- The toxicological profile of carbon dioxide is well established with a substantial amount of data. Although this information has its limitations and it does not address the issue of fertility and reproduction specifically, it is considered sufficient to address the toxicity of carbon dioxide particularly given the low level of exposure expected from its use as a rodenticide.
- Carbon dioxide is a potential basic substance as referred to in Article 2(1c) of Directive 98/8/EC and will be dealt with accordingly.