ANNEX

PART A

CHEMICAL ACTIVE SUBSTANCES

SECTION 5

Toxicological and metabolism studies

5.5. Long-term toxicity and carcinogenicity

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

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

— identify target organs, where relevant,

— establish the dose-response relationship,

— establish the NOAEL and, if necessary, other appropriate reference points.

Correspondingly, the results of the carcinogenicity studies taken together with other relevant data and information on the active substance, shall be sufficient to permit the evaluation of hazards for humans, following repeated exposure to the active substance, and in particular shall be sufficient:

(a) to identify carcinogenic effects resulting from long-term exposure to the active substance;

(b) to establish the species, sex, and organ specificity of tumours induced;

(c) to establish the dose-response relationship;

(d) where possible, to identify the maximum dose eliciting no carcinogenic effect;

(e) where possible, to determine the mode of action and human relevance of any identified carcinogenic response.

Circumstances in which required

The long-term toxicity and carcinogenicity of all active substances shall be determined. If in exceptional circumstances it is claimed that such testing is unnecessary, that claim shall be fully justified.

Test conditions

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

A second carcinogenicity study of the active substance shall be conducted using mouse as test species, unless it can be scientifically justified that this is not necessary. In such cases, scientifically validated alternative carcinogenicity models may be used instead of a second carcinogenicity study.

If comparative metabolism data indicate that either rat or mouse is an inappropriate model for human cancer risk assessment, an alternative species shall be considered.

Experimental data, including the elucidation of the possible mode of action involved and relevance to humans, shall be provided where the mode of action for carcinogenicity is considered to be non-genotoxic.

Where submitted, historical control data shall be from the same species and strain, maintained under similar conditions in the same laboratory and shall be from contemporaneous studies. Additional historical control data from other laboratories may be reported separately as supplementary information.

The information on historical control data provided shall include:

(a) identification of species and strain, name of the supplier, and specific colony identification, if the supplier has more than one geographical location;

(b) name of the laboratory and the dates when the study was performed;

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

(d) approximate age, in days, and weight of the control animals at the beginning of the study and at the time of killing or death;

(e) description of the control group mortality pattern observed during or at the end of the study, and other pertinent observations (such as diseases, infections);

(f) name of the laboratory and the examining scientists responsible for gathering and interpreting the pathological data from the study;

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

The historical control data shall be presented on a study by study basis giving absolute values plus percentage and relative or transformed values where these are helpful in the evaluation. If combined or summary data are submitted, these shall contain information on the range of values, the mean, median and, if applicable, standard deviation.

The doses tested, including the highest dose tested, shall 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. Dose selection should consider toxicokinetic data such as saturation of absorption measured by systemic availability of active substance and/or metabolites.

Doses, causing excessive toxicity shall not be considered relevant to evaluations to be made. Determination of blood concentration of the active substance (for example around T_{max}) shall be considered in long-term studies.

In the collection of data and compilation of reports, incidence of benign and malignant tumours shall not be combined. Dissimilar, un-associated tumours, whether benign or malignant, occurring in the same organ, shall not be combined for reporting purposes.

In the interests of avoiding confusion, conventional histopathological terminology commonly used when the study is conducted such as that published by the International Agency for Research on Cancer shall be used in the nomenclature and reporting of tumours. The system used shall be identified.

Biological material selected for histopathological examination shall include 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, might be of value, and when conducted, shall be reported.

Changes to legislation:
There are outstanding changes not yet made to Commission Regulation (EU) No 283/2013. Any changes that have already been made to the legislation appear in the content and are referenced with annotations.
View outstanding changes

Changes and effects yet to be applied to the whole legislation item and associated provisions

- Signature words omitted by S.I. 2019/556 reg. 21(4)
- Annex Pt. A s. 8 word omitted by S.I. 2019/556 reg. 21(5)(b)(xiv)
- Annex Pt. A s. 1 point 1.4 word substituted in earlier amending provision S.I. 2019/720, Sch. 2 para. 176(2)(a)(i) by S.I. 2020/1567 Sch. 2 para. 61
- Annex Pt. A s. 1 point 1.4.1 word substituted in earlier amending provision S.I. 2019/720, Sch. 2 para. 176(2)(b) by S.I. 2020/1567 Sch. 2 para. 61
- Annex Pt. B s. 9 words omitted by S.I. 2019/556 reg. 21(5)(c)(vi)
- Art. 1(1) Art. 1 renumbered as Art. 1(1) by S.I. 2019/556 reg. 21(2)(a)
- Art. 1(2) inserted by S.I. 2019/556 reg. 21(2)(b)