ANNEX

PART A

CHEMICAL ACTIVE SUBSTANCES

SECTION 6

Residues in or on treated products, food and feed

6.2. Metabolism, distribution and expression of residues

Data on metabolism representative for existing or intended good agricultural practices (GAPs) shall be provided, together with a schematic diagram of the metabolic pathways in plants and animals with a brief explanation of the distribution and chemical reactions involved. These studies shall be conducted with one or more radio-labelled forms of the active substance and, where relevant, stereoisomer forms of the active substance and its metabolites. For plant extracts, a different approach may be taken if adequately justified.

For plants, the objectives of these studies shall be:

(a) to provide an estimate of total terminal residues in the relevant portion of crops at harvest following treatment as proposed;

(b) to identify the major components of the total terminal residue;

(c) to indicate the distribution of residues between relevant crops parts;

(d) to quantify the major components of the residue and to show the efficiency of extraction procedures for these components;

(e) to characterise and quantify conjugated and bound residues;

(f) to indicate the components to be analysed for in residue quantification studies (crop residue studies).

For food producing animals, the objectives of these studies shall be:

(a) to provide an estimate of total terminal residues in edible animal products;

(b) to identify the major components of the total terminal residue in edible animal products;

(c) to indicate the distribution of residues between relevant edible animal products;

(d) to provide evidence whether or not a residue should be classified as fat soluble;

(e) to quantify the total residue in certain animal products (milk or eggs) and excreta;

(f) to quantify the major components of the residue and to show the efficiency of extraction procedures for these components;

(g) to characterise and quantify conjugated and bound residues;

(h) to indicate the components to be analysed for in residue quantification studies (livestock feeding studies);

(i) to generate data from which a decision on the need for feeding studies on food producing animals can be made.

The results of the metabolism study conducted with poultry, normally laying hens, shall be extrapolated to all food producing poultry whereas the results of the metabolism study conducted with ruminants, normally lactating goats and, where necessary, with pigs, shall be extrapolated to all food producing mammals.

Metabolites not found in the ADME studies or that cannot be explained as intermediates, but identified in metabolism/transformation studies (plant, food producing animals, processing and rotational crops) shall be considered relevant for the consumer risk assessment, unless it can be demonstrated by scientific evidence (such as structure-activity relationship, toxicological bridging studies) that, also in view of their concentration, they cause no potential risks to the consumer.

6.2.1. *Plants*
Circumstances in which required

Studies on plants shall be performed unless no part of the plants or plant products will be used as food or feed material or unless a 'zero' residue situation applies (such as bait applications).
Test conditions

The intended method of application (such as seed treatment, soil/foliar spraying, dipping, fogging) and the properties of the active substance (such as systemic properties or volatility) shall be taken into account when planning metabolism studies. Metabolism studies have to involve crops from different categories of crops in which plant protection products containing the active substance in question would be used. For this purpose crops shall be considered as falling into one of the following categories:

(a) fruit (code F);

(b) root crops (code R);

(c) leafy crops (code L);

(d) cereal/grass crops (code C/G);

(e) pulses and oilseeds (code P/O);

(f) miscellaneous.

The category 'miscellaneous' shall only be used on a case by case basis.

A metabolism study shall be submitted for each type of crop group for which use is proposed. In order to extrapolate results from metabolism studies with an active substance to all crop groups, metabolism studies on a minimum of three representative crops (from the different crop groups except 'miscellaneous') shall be conducted. If the results of these three studies indicate a comparable metabolic route (qualitatively and to a lesser extent quantitatively), then additional studies shall not be needed. If the results from the available studies from three of these categories indicate that the route of degradation is not similar in all three categories, studies from the remaining categories except 'miscellaneous' shall be provided.

If authorisation is sought for one crop group only, metabolism studies in one crop from that crop group shall be sufficient as long as the crop is truly representative of the crop group and the metabolic pathway is elucidated.

The studies shall reflect the intended use pattern of the active ingredient such as foliar, soil/seed or post-harvest treatments. If, for instance, three studies have been conducted using foliar

application and at a later date soil application (such as seed treatment, granular or soil drench) is proposed, then at least one additional study reflecting soil application shall be conducted. The applicant shall discuss with the national competent authorities the possible replacement of a foliar study with a post-harvest study.

An evaluation of the results from different studies shall be submitted on:

(a) the site of uptake (for example via leaves or roots);

(b) the formation of metabolites and breakdown products;

(c) the distribution of residues between relevant parts of the crop at harvest (with particular emphasis on food and feed);

(d) the metabolic pathways.

If studies show that the active substance or relevant metabolites or breakdown products are not taken up by the crop, a rationale shall be given.

6.2.2. *Poultry*
Circumstances in which required

Metabolism studies on poultry shall be provided where the plant protection product is to be used in crops whose parts or products, also after processing, are fed to poultry and where the intake is expected to exceed 0,004 mg/kg bw/day[(1)].
Test conditions

Studies shall be carried out in laying hens.

Dose rates shall be at least equivalent to the likely maximum daily exposure resulting from all intended uses.

If the identification of metabolites cannot be carried out with dose rates of 10 mg/kg feed (dry matter), higher doses may be used.

If no feeding studies are carried out, plateau levels in eggs shall be demonstrated in the metabolism study taking into account that plateau levels usually occur no later than 14 days from the beginning of dosing in laying poultry.

6.2.3. *Lactating ruminants*
Circumstances in which required

Metabolism studies on lactating ruminants shall be provided where the plant protection product is to be used in crops whose parts or products, also after processing, are fed to ruminants and where the intake is expected to exceed 0,004 mg/kg bw/day.
Test conditions

Studies shall be carried out in lactating goats, where available, or in lactating cows as an alternative.

Dose rates shall at least be equivalent to the likely maximum daily exposure resulting from all intended uses.

If the identification of main metabolites cannot be carried out with dose rates of 10 mg/kg feed (dry matter), higher doses may be used.

If no feeding studies are carried out, plateau levels in milk shall be demonstrated in the metabolism study taking into account that plateau levels usually occur five to seven days after the beginning of dosing in lactating ruminants.

6.2.4. *Pigs*
Circumstances in which required

Metabolism studies on pigs shall be provided where the plant protection product is used in crops whose parts or products, also after processing, are fed to pigs and where it becomes apparent that metabolic pathways differ significantly in the rat as compared to ruminants and where the intake is expected to exceed 0,004 mg/kg bw/day.
Test conditions

Studies shall be carried out in pigs.

Dose rates shall at least be equivalent to the likely maximum daily exposure resulting from all intended uses.

If the identification of metabolites cannot be carried out with dose rates of 10 mg/kg feed (dry matter), higher doses may be used.

The duration of this study shall be the same as for lactating ruminants.

6.2.5. *Fish*
Circumstances in which required

Metabolism studies on fish may be required where the plant protection product is used in crops whose parts or products, also after processing, are fed to fish and where residues in feed may occur from the intended applications.

Results from studies provided for under point 8.2.2.3 may be used if it can be demonstrated with scientific evidence that the results of these studies may be assumed to be equivalent. Special consideration shall be given to the different routes of ingestion.

(**1**) mg/kg bw/day = mg active substance / kg body weight of the concerned species / day.

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)