Integrated testing strategy for repeated dose toxicity under REACH

10-100 tonnes per year band

The substance is manufactured or imported in quantities ≥ 10 tonnes per year

A reliable sub-chronic (90 days) or chronic toxicity study is available, provided that an appropriate species, dosage, solvent and route of administration were used;
OR
the substance undergoes immediate disintegration and there are sufficient data on the cleavage products.

No

Yes

The frequency and duration of human exposure indicates that a longer term study (>28 days) is appropriate;
AND:
– other available data indicate that the substance may have a dangerous property that cannot be detected in a short-term toxicity study;
OR
– appropriately designed toxicokinetic studies reveal accumulation of the substance or its metabolites in certain tissues or organs which would possibly remain undetected in a short-term toxicity study but which are liable to result in adverse effects after prolonged exposure.

No

Yes

Propose[1] the sub-chronic toxicity study (90 days), annex IX, section 8.6.2, see ITS for 100-1000 tonnes per year band.

Choose appropriate route of administration, having regard to the likely route of human exposure.

Inhalation of the substance is unlikely;
AND
skin contact in production and/or use is likely;
AND
the physicochemical and toxicological properties suggest potential for a significant rate of absorption through the skin.

No

Exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size.

No

Perform[1] short-term repeated dose toxicity study (28 days) by the oral route, one species, male and female.

Yes

Perform[1] short-term repeated dose toxicity study (28 days) by the dermal route, one species, male and female.

Yes

Perform[1] short-term repeated dose toxicity study (28 days) by the inhalation route, one species, male and female.

Identifying a NOAEL in the 28 or the 90 days study failed, unless the reason for this is absence of adverse toxic effects;
OR
there is a toxicity of particular concern (e.g. serious/severe effects);
OR
there are indications of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation (in such cases it may also be more appropriate to perform specific toxicological studies that are designed to investigate these effects, e.g. immunotoxicity, neurotoxicity);
OR
the route of exposure used in the initial repeated dose study was inappropriate in relation to the expected route of human exposure and route-to-route extrapolation cannot be made;
OR
there is a particular concern regarding exposure (e.g. use in consumer products leading to exposure levels which are close to the dose levels at which toxicity to humans may be expected);
OR
some effects shown with substances with a clear relationship in molecular structure with the substance being studied, were not detected in the 28 or the 90 days study.

Yes

Propose[1,2] further studies.

No

The substance is manufactured or imported in quantities ≥ 100 tonnes per year

No

No further testing required.

Yes

Continue ITS for ≥ 100 tonnes per year (2/3)

1. A registrant may adapt the standard testing regime in accordance with the general rules set out in annexe XI section 1 (Testing does not appear scientifically necessary) and 2 (Testing is technically not possible). Under dossier evaluation the Agency may assess these adaptations to the standard testing regime. Furthermore, testing may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report as mentioned in annexe XI, section 3 (Substance-tailored exposure-driven testing).

2. These studies may also be required by the Agency.

cnrs

Prévention du risque chimique, France, 2007

REACH Registration, Evaluation, Authorisation of Chemicals

Integrated testing strategy for repeated dose toxicity under REACH

2/3

100-1000 tonnes per year band

The substance is manufactured or imported in quantities ≥ 100 tonnes per year

A reliable short-term toxicity study (28 days) is available showing severe toxicity effects according to the criteria for classifying the substance as R48, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure;

OR

a reliable chronic toxicity study is available, provided that an appropriate species and route of administration were used;

OR

the substance undergoes immediate disintegration and there are sufficient data on the cleavage products (both for systemic effects and effects at the site of uptake);

OR

the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and no evidence of toxicity in a 28-day "limit test", particularly if such a pattern is coupled with limited human exposure.

No

Choose appropriate route of administration, having regard to the likely route of human exposure.

Skin contact in production and/or use is likely;

AND

the physicochemical properties suggest a significant rate of absorption through the skin;

AND

– toxicity is observed in the acute dermal toxicity test at lower doses than in the oral toxicity test; **OR**
– systemic effects or other evidence of absorption is observed in skin and/or eye irritation studies; **OR**
– *in vitro* tests indicate significant dermal absorption; **OR**
– significant dermal toxicity or dermal penetration is recognised for structurally-related substances.

Yes

Propose[1] the sub-chronic toxicity study (90-day), by the dermal route, one species, rodent, male and female.

No

Exposure of humans via inhalation is likely taking into account the vapour pressure of the substance and/or the possibility of exposure to aerosols, particles or droplets of an inhalable size.

Yes

Propose[1] the sub-chronic toxicity study (90-day), by the inhalation route, one species, rodent, male and female.

No

Propose[1] the sub-chronic toxicity study (90-day), by the oral route, one species, rodent, male and female.

Yes

A short-term repeated dose toxicity study (28 days), one species, male and female, most appropriate route of administration, having regard to the likely route of human exposure, is already provided.

Yes

No

Propose[1] a short-term repeated dose toxicity study (28 days), one species, male and female, most appropriate route of administration, having regard to the likely route of human exposure. In this case, section 3 of Annexe XI shall not apply.

Identifying a NOAEL in the 90 days study failed unless the reason for the failure to identify a NOAEL is absence of adverse toxic effects;

OR

there is a toxicity of particular concern (e.g. serious/severe effects);

OR

There are indications of an effect for which the available evidence is inadequate for toxicological and/or risk characterisation (in such case, it may also be more appropriate to perform specific toxicological studies that are designed to investigate these effects, e.g. immunotoxicity, neurotoxicity);

OR

there is particular concern regarding exposure (e.g. use in consumer products leading to exposure levels which are close to the dose levels at which toxicity to humans may be expected).

Yes

Propose[1, 2] further studies.

No

The substance is manufactured or imported in quantities ≥ 1000 tonnes per year

No

No further testing required.

Yes

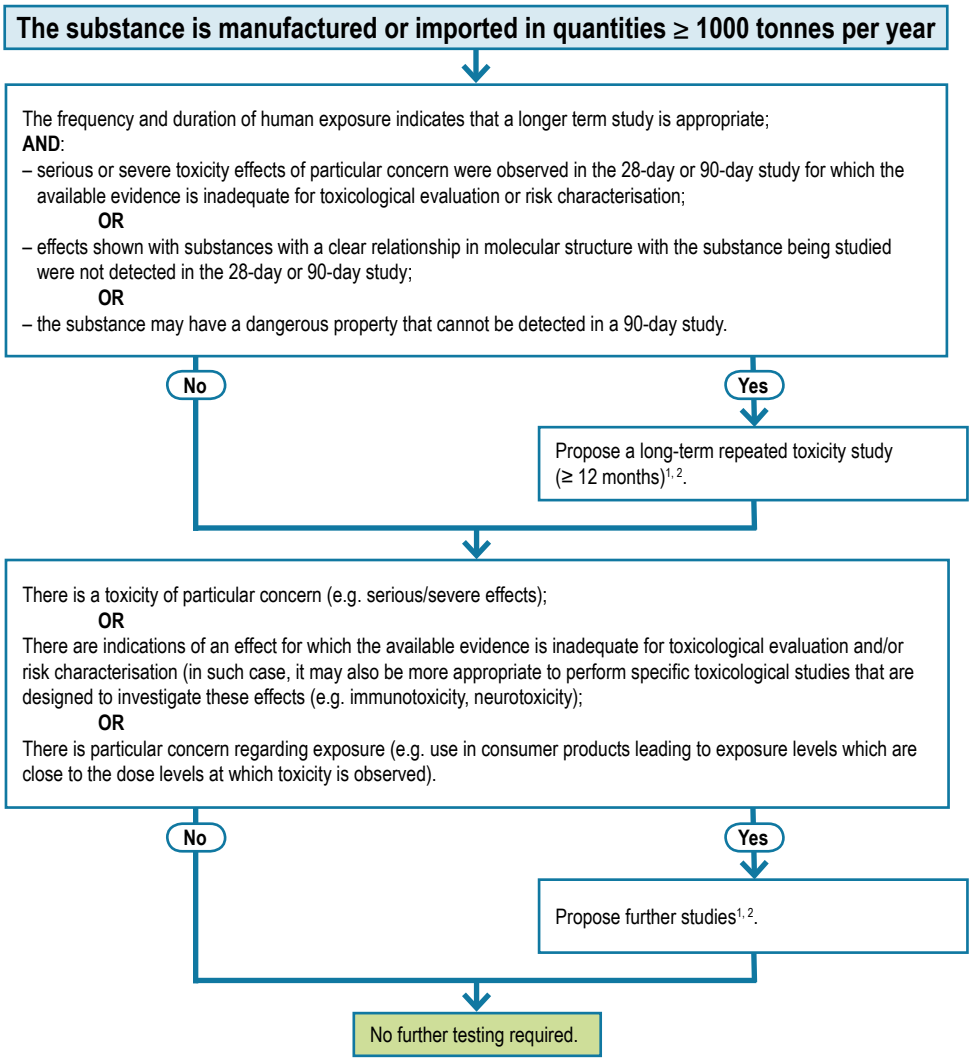
Continue ITS for ≥ 1000 tonnes per year (3/3)

1. A registrant may adapt the standard testing regime in accordance with the general rules set out in annexe XI section 1 (Testing does not appear scientifically necessary) and 2 (Testing is technically not possible). Under dossier evaluation the Agency may assess these adaptations to the standard testing regime. Furthermore, testing may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report as mentioned in annexe XI, section 3 (Substance-tailored exposure-driven testing).

2. These studies may also be required by the Agency.

Integrated testing strategy for repeated dose toxicity under REACH

≥ 1000 tonnes per year band



1. A registrant may adapt the standard testing regime in accordance with the general rules set out in annexe XI section 1 (Testing does not appear scientifically necessary) and 2 (Testing is technically not possible). Under dossier evaluation the Agency may assess these adaptations to the standard testing regime. Furthermore, testing may be omitted, based on the exposure scenario(s) developed in the Chemical Safety Report as mentioned in annexe XI, section 3 (Substance-tailored exposure-driven testing).

2. These studies may also be required by the Agency.