[X1ANNEX IX

STANDARD INFORMATION REQUIREMENTS FOR SUBSTANCES MANUFACTURED OR IMPORTED IN QUANTITIES OF 100 TONNES OR MORE (1)

Editorial Information

X1 Substituted by Corrigendum to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC (Official Journal of the European Union L 396 of 30 December 2006).

8. TOXICOLOGICAL INFORMATION

COLUMN 1 STANDARD INFORMATION REQUIRED	COLUMN 2 SPECIFIC RULES FOR ADAPTATION FROM COLUMN 1
	8.4. If there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII and there are no results available from an *in vivo* study already, an appropriate *in vivo* somatic cell genotoxicity study shall be proposed by the registrant. If there is a positive result from an *in vivo* somatic cell study available, the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered.
8.6. Repeated dose toxicity	
8.6.1. 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, unless already provided as part of Annex VIII requirements or if tests according to Section 8.6.2 of this Annex is proposed. In this case, Section 3 of Annex XI shall not apply.	
[F1 8.6.2. Sub-chronic toxicity study (90-day), one species, rodent, male and female, most appropriate route of	8.6.2. The sub-chronic toxicity study (90 days) does not need to be conducted if:

administration, having regard to the likely route of human exposure.	— 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 — a 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. The appropriate route shall be chosen on the following basis: Testing by the dermal route is appropriate if: (1) skin contact in production and/or use is likely; and (2) the physicochemical properties suggest a significant rate of absorption through the skin; and (3) one of the following conditions is met: — 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.

	Testing by the inhalation route is appropriate if: — 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. For nanoforms toxicokinetics shall be considered including recovery period and, where relevant, lung clearance. Further studies shall be proposed by the registrant or may be required by the Agency in accordance with Articles 40 or 41 in case of: — failure to identify a NOAEL in the 90 days study unless the reason for the failure to identify a NOAEL is absence of adverse toxic effects, or — toxicity of particular concern (e.g. serious/severe effects), or — 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, and in particular for nanoforms indirect genotoxicity), or — 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).]
8.7. Reproductive toxicity	8.7. The studies do not need to be conducted if: — the substance is known to be a genotoxic carcinogen and appropriate risk management measures are implemented, or — the substance is known to be a germ cell mutagen and appropriate risk management measures are implemented, or — the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven

		from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure. **[**F2If a substance is known to have an adverse effect on fertility, meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage fertility (H360F), and the available data are adequate to support a robust risk assessment, then no further testing for fertility will be necessary. However, testing for developmental toxicity must be considered. If a substance is known to cause developmental toxicity, meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary. However, testing for effects on fertility must be considered.**]**
8.7.2.	Pre-natal developmental toxicity study, one species, most appropriate route of administration, having regard to the likely route of human exposure (B.31 of the Commission Regulation on test methods **[**F3made under**]** Article 13(3) or OECD 414).	8.7.2. The study shall be initially performed on one species. A decision on the need to perform a study at this tonnage level or the next on a second species should be based on the outcome of the first test and all other relevant available data.
[F4 8.7.3.	Extended One-Generation Reproductive Toxicity Study (B.56 of the Commission Regulation on test methods **[**F5made under**]** Article 13(3) or OECD 443), basic test design (cohorts 1A and 1B without extension to include a F2 generation), one species, most appropriate route of administration, having regard to the likely route of human exposure, if the available repeated dose toxicity studies (e.g. 28-day or 90-day studies, OECD 421 or 422 screening	8.7.3. An Extended One-Generation Reproductive Toxicity Study with the extension of cohort 1B to include the F2 generation shall be proposed by the registrant or may be required by the Agency in accordance with Article 40 or 41, if: (a) the substance has uses leading to significant exposure of consumers or professionals, taking into account, inter alia, consumer exposure from articles, and (b) any of the following conditions are met:

studies) indicate adverse effects on reproductive organs or tissues or reveal other concerns in relation with reproductive toxicity.	— the substance displays genotoxic effects in somatic cell mutagenicity tests *in vivo* which could lead to classifying it as Mutagen Category 2, or — there are indications that the internal dose for the substance and/or any of its metabolites will reach a steady state in the test animals only after an extended exposure, or — there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies or non-animal approaches. An Extended One-Generation Reproductive Toxicity Study including cohorts 2A/2B (developmental neurotoxicity) and/or cohort 3 (developmental immunotoxicity) shall be proposed by the registrant or may be required by the Agency in accordance with Article 40 or 41, in case of particular concerns on (developmental) neurotoxicity or (developmental) immunotoxicity justified by any of the following: — existing information on the substance itself derived from relevant available *in vivo* or non-animal approaches (e.g. abnormalities of the CNS, evidence of adverse effects on the nervous or immune system in studies on adult animals or animals exposed prenatally), or — specific mechanisms/modes of action of the substance with an association to (developmental) neurotoxicity and/or (developmental) immunotoxicity (e.g. cholinesterase inhibition or relevant changes in thyroidal hormone levels associated to adverse effects), or — existing information on effects caused by substances structurally analogous to the substance being studied, suggesting such effects or mechanisms/modes of action.

	Other studies on developmental neurotoxicity and/or developmental immunotoxicity instead of cohorts 2A/2B (developmental neurotoxicity) and/or cohort 3 (developmental immunotoxicity) of the Extended One-Generation Reproductive Toxicity Study may be proposed by the registrant in order to clarify the concern on developmental toxicity. Two-generation reproductive toxicity studies (B.35, OECD TG 416) that were initiated before 13 March 2015 shall be considered appropriate to address this standard information requirement. The study shall be performed on one species. The need to perform a study at this tonnage level or the next on a second strain or a second species may be considered and a decision should be based on the outcome of the first test and all other relevant available data.**]]**

(1) **[**[X1]This Annex shall apply to producers of articles that are required to register in accordance with Article 7 and to other downstream users that are required to carry out tests under this Regulation adapted as necessary.**]**

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Changes to legislation:
There are currently no known outstanding effects for the Regulation (EC) No 1907/2006 of the European Parliament and of the Council, Division 8. .