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EU STRATEGY FOR A FUTURE CHEMICALS POLICY: REACH

9. REGISTRATION SAFETY DATA

The information on hazardous properties, as specified in Annexes V to VIII, is linked to the manufacture/import level, on the grounds that there is a potential for more exposure as more substance is in the EU (Tables 5 to 8). The Annexes specify the standard data requirements and give rules on the circumstances in which data may be omitted and when extra data are triggered. The compromise text agreed a targeted approach for registration of phase-in substances at 1 to 10 tonnes per annum, using criteria given in Annex Ic of the Regulation. Full Annex V test data are only needed if the phase-in substance meets the PBT or vPvB criteria, is predicted to be classified as a CMR or is predicted to be classified as dangerous to human health or the environment with dispersive or diffuse use, particularly if used by consumers. Otherwise only available safety data have to be included in the registration, together with the full set of Annex V physico-chemical tests, although these do not have to be conducted in compliance with Good Laboratory Practice (GLP). New substances at 1 to 10 tonnes per annum require full Annex V data.

New animal studies are required only if surrogate data or in vitro alternative tests cannot provide the necessary information. All new studies are to be GLP compliant and conducted to standard EU (or OECD) methods. Safety studies and risk assessment are summarised by D J Knight and M B Thomas [14].

Registrants have to update the ECA with any change in their status, or composition of the substance, significant changes in tonnage, new uses, significant new knowledge on risks, any change in classification and labelling and any update to the CSR.

Table 6 Annex VI Data for Substances at ≥ 10 tonnes per annum

In addition to the Annex V data:

In vivo skin irritation (unless classified from Annex V data)
In vivo eye irritation (unless classified from Annex V data)
In vitro chromosome aberration test
In vitro gene mutation assay
Acute inhalation or dermal toxicity
28-day (or 90-day) repeat-dose study in the rat (normally oral exposure)
Toxicokinetics assessment (a prediction based on the available data)
Acute fish toxicity
Algal growth test
Activated sludge respiration inhibition test
Hydrolysis test
Adsorption/desorption screening test

Possible additional studies:
In vivo mutagenicity studies
Further repeat-dose study in the rat
Developmental toxicity study
Two-generation fertility study in the rat
Chronic fish toxicity study
Biodegradation simulation studies

Table 7 Annex VII Data for Substances at ≥ 100 tonnes per annum

The registrant makes a testing programme proposal covering:
Stability in organic solvents and identification of degradants
Dissociation constant
Viscosity
Reactivity to container material
In vivo mutagenicity studies

90-day repeat-dose study in the rat (if not part of the Annex VI data)
Developmental toxicity studies in two species
Two-generation fertility study in the rat

21-day *Daphnia* reproduction study
Chronic fish toxicity study
Simulation test on the ultimate degradation in surface water
Soil simulation test
Sediment simulation test
Fish bioaccumulation study (unless there is a low predicted bioaccumulation potential, e.g. from Log P_{ow} < 3)
Further adsorption/desorption study
14-day earthworm toxicity
Study of the effects on soil micro-organisms
Short-term toxicity to plant

Table 8 Annex VIII Data for Substances at ≥ 1,000 tonnes per annum

The registrant makes a testing programme covering, if appropriate:
Further mutagenicity studies
Long-term repeat-dose (≥ 12 months) study in the rat
Further toxicity study to investigate specific concerns
Two-generation fertility study in the rat (if not part of the Annex VII data)
Carcinogenicity study (often combined with a 2-year chronic toxicity study, usually in the rat)
Further biodegradation in water, sediment and soil – covering degradation rate and identification of relevant degradants
Further environmental fate and behaviour studies
Long-term earthworm toxicity
Long-term toxicity to other soil invertebrates
Long-term plant toxicity
Long-term toxicity to sediment organisms
Long-term or reproductive bird toxicity

Any studies that are technically impossible clearly can be omitted. In addition to the specific rules, the registrant can adapt the required standard information and provide the data using other information, such as non-standard or non-GLP tests, historical human data, a weight of evidence, structure activity relationships (SAR) or 'read-across' to tested analogues. Guidance on using such surrogate data is given in Annex IX (Table 9). This includes a provision for 'substance-tailored exposure-driven testing' to allow for reduced Annex VII and VIII animal testing for low exposure evaluated substances. The compromise text has introduced the possibility of exposure-based data waivers to Annex VI data for substances registered at 10 tonnes per annum. There is a guidance note in Annex IV on fulfilling the data requirements of Annex V to VIII. The registrant is advised to gather and share existing information, consider the information needs, identify information gaps and only then generate the missing data for registration at 1 or 10 tonnes per annum or propose further testing at 100 or 1,000 tonnes per annum.

Table 9 Registration Safety Data

- Annexes V to VIII give standard data requirements (in column 1) and rules for omitting tests or additional studies (in column 2)
- Annex IX covers adapting the standard data requirements:
  - existing non-standard and/or non-GLP data
  - historical human data
  - weight of evidence
  - SAR
  - grouping and "read across"
  - suitable in vitro tests, but confirmation of negative results may be needed from non-validated in vitro methods
  - data waivers, ie. a study is technically impossible
  - substance-tailored exposure driven testing

10. DATA PROTECTION, DATA SHARING AND THE ONE SUBSTANCE ONE REGISTRATION APPROACH

The ECA will establish and maintain a publicly-accessible database of registered substances, with a short profile of hazardous properties, labelling and other EU legislation that applies.

The registrant can claim most information confidential (Table 10), and the ECA or Competent Authority who receives the information evaluates the confidentiality claim. Non-confidential information is made available to the public over the Internet. The compromise text gives improved measures for protecting information published on the ECA website: the registrant can request that the robust summaries, study summaries and supply tonnage band are not included in the public database, but this information would be available to the public on request.

Table 10 (See Column 2)

Registrants can check the ECA database before conducting animal studies, and also make a data-sharing enquiry to find out if a new substance has already been registered. If the substance has already been registered, studies submitted ≥ 10 years before can be used as of right for the new registration. Studies submitted less than 10 years before are still protected, but the two parties are put into contact with a view to reaching an agreement to share data. Animal studies cannot be repeated, and the idea of the scheme is for the second registrant to pay a proportion of the costs of the animal studies to their owner.

Table 10 Confidentiality Provisions

The registrant cannot claim confidentiality for:

- trade name and chemical name
- physico-chemical properties and the result of toxicology and ecotoxicology studies (and the determined PNEL/PNEC)
- purity and impurity (if relevant to classification)
- guidance on safe use
- non-confidential SDS information
- analytical methods for detection in humans or the environment
- fact that animal testing was conducted

In order to allow the data-sharing scheme to operate for existing phase-in substances, there is a duty to pre-register such substances with the ECA within 6 months, beginning 12 months after the Regulation comes into force. The information in the pre-registration is the identity of the substance and registrant and a listing of the existing physico-chemical and safety data, including a short description of animal studies. There is also the option voluntarily to pre-register substances at < 1 tonne per annum. All pre-registrants for a particular phase-in substance are participants in a substance information exchange forum (SIEF), and therefore the mandatory data-sharing/data-compensation scheme can operate for animal studies. If a particular study is not available within the SIEF, participants must reach an agreement to conduct a single study and avoid duplicate animal testing. A new supplier of a phase-in substance can begin supply and join the review programme.

The compromise text adopted the OSOR proposal: the aim is to have one combined registration dossier for a particular substance, with combined information from all the registrants. Information on the identity of the registrant and substance and confidentiality claims is submitted separately to the ECA by each registrant. However, there is the possibility of opting out of submitting a joint registration dossier if the cost would be disproportionate, where there would be a breach of confidentiality or if there is a disagreement between registrants on selection of the classification or safety data. Nevertheless, sharing of animal testing is still mandatory, as is sharing of non-animal testing if requested by one potential registrant.

11. COSTS OF TESTING FOR REACH

The overall initial cost of testing substances for registration under REACH depends on the tonnage, with data to be provided in advance of supply at ≥ 1 and ≥ 10 tonnes per annum. Compared with the current DSD notification scheme, the Annex Vdata-set is effectively an extended 'reduced notification' (i.e. including some "base set" tests) and Annex VI is approximately a 'base set' (i.e. with some Level 1 studies). For supply at ≥ 100 and ≥ 1,000 tonnes per annum the testing programme is negotiated with the Competent Authority, and hence the costs will be highly variable. These Annex VII and VIII data comprise the current Level 1 and 2 studies respectively, with various additions and modifications. In practice there is likely to be ample opportunity to reduce testing costs by sharing data and making use of surrogate data and data waivers for many chemicals. However, there will be some cases where extra testing is triggered from the results of the standard tests or as an outcome of risk assessment. Therefore it is difficult to compare the cost of registration with the current notification scheme, but Table 11 (See page III) describes the standard notification testing to put the REACH data into context.

Table 11 Current Notification Studies

Reduced notification for substances at ≥ 0.1 tonne per annum (or ≥ 0.5 tonnes cumulative): Annex VII B of the Directive [3]

Melting/freezing point
Boiling point
Water solubility
n-Octanol-water partition coefficient
Flash point or flammability

Possible additional studies:
Vapour pressure

Acute Daphnia toxicity
Acute oral toxicity
Skin irritation
Eye irritation
Skin sensitisation
Ames test
Ready biodegradation

Base Set for substances at ≥ 1 tonne per annum (or ≥ 5 tonnes cumulative): Annex VII A of the Directive [3]:

Melting/freezing point
Boiling point
Relative density
Vapour pressure
Water solubility
n-Octanol-water partition coefficient
Surface tension
Flash point or flammability
Explosivity
Auto-flammability Oxidising properties
Granulometry
Acute oral toxicity Acute dermal and/or inhalation toxicity

Skin irritation
Eye irritation
Skin sensitisation
28-Day repeat dose study in the rat
Ames test
in vitro gene mutation or chromosome aberration test
Toxicokinetics assessment (a prediction based on the available data)Acute fish toxicity
Acute daphnia toxicity
Algal growth test
Ready biodegradation
Activated sludge respiration inhibition test
Hydrolysis test
Adsorption/desorption screening test

Level 1 for substances at 100 tonnes per annum (or 500 tonnes cumulative), possibly with some studies before: Annex VIII of the Directive [3]

One- or two-generation fertility study in the rat
Developmental toxicity study
90-Day repeat-dose study in the rat
Further mutagenicity study
Basic toxicokinetic information
21-Day Daphnia reproduction study
Chronic fish toxicity study

Fish bioaccumulation study (or prediction)
14-Day earthworm toxicity study
Test on higher plants
Further biodegradation test
Further adsorption/desorption study
Sediment dwelling organism toxicity study

Level 2 for substances at ≥ 1000 tonnes per annum (or ≥ 5000 tonnes cumulative): Annex VIII of the Directive [3]:

It is not possible to define exactly what testing is required at Level 2, because this depends upon the Level 1 results and Risk Assessment at Base Set and Level 1.

12. PREPARING FOR REACH

The chemical industry operating in the EU will be greatly affected by REACH, and there will be ramifications worldwide. The uncertainty in key final aspects of REACH and when the scheme will begin operating make it challenging for industry to plan how to prepare for REACH and develop budgets for the costs of new studies and registration work. It is certain, however, that considerable resources will be needed. In practice chemical companies should begin preparing for REACH as soon as possible to avoid being caught out by unanticipated costs, regulatory hurdles and loss of important chemicals.

A first step is to develop inventories of chemical substances supplied and purchased, including components of preparations. For purchased substances, the next stage is to try and find out if the supplier is planning to support the substance, in particular by registering the purchaser's use and including this in the risk assessment of the CSR. There are almost certain to be some unsupported substances in each company's inventory of purchased chemicals. A supplier of chemicals will have to decide which to support, and make plans to withdraw any that will no longer be profitable. To do this an evaluation of what existing safety data are available is an essential first step, taking into account in-house studies and literature data. This will enable a data gap analysis for registration to be drafted, based on whether Annex V or Annex VI standard data are needed for the initial registration (Tables 5 and 6 respectively). This data gap analysis can be refined to evaluate the reliability of any literature data and judge whether the existing information can be used for the

registration and to decide if 'read across' or other surrogate data can be used, to get an indication of the initial cost to register the 'phase-in' substance. At the pre-registration stage, however, it may turn out that other companies are supporting the substance, with the opportunity to use their data and share the cost of developing new studies.

Registration dossiers for substances at below 100 tonnes per annum will not be evaluated, so it is up to the registrant to make the case for using non-standard data and surrogate data. If and when the substance is evaluated, however, it may turn out that some new studies are needed to complete the basic Annex VI data package, and there will certainly be extra cost for the Annex VII and VIII data (Tables 7 and 8). In addition, there will be some 'very high concern' chemicals for which uses have to be authorised. Many of these will already be known, because the CMR classifications are already established. Others substances for authoisation will be identified as the initial registration data are developed and collated.

Intelligent safety evaluation will be especially important for the new EU REACH scheme. Decisions have to be made on whether to use literature data and/or "surrogate data" and if "data waivers" are appropriate. With other registration schemes, there is the opportunity to consult the particular competent authority evaluating the substance before the registration dossier is submitted. In contract with REACH registrations the dossier is submitted to the ECA, and initially there is only to be an administrative check. Therefore it will probably be left to the registrant to decide on the final testing programme for new studies under REACH. Nevertheless, certain substances will be evaluated under the REACH scheme in detail by a rapporteur competent authority on behalf of the EU with a view to further testing. In these circumstances it will be useful to base these discussions on the risk assessment included in the original registration in the CSR, supported by appropriate expert reports if necessary to improve the scientific arguments of the case.

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