## 1. Background

In October 1989 the OECD organized, in the context of that organizations chemicals programme, a workshop on notification schemes for new chemicals. The major objective of this meeting was to review, in the light of the 1981 OECD Council Act on the Mutual Acceptance of Data, the notification schemes applied by the Member Countries of the OECD. The 1981 Council Act recommended that countries require manufacturers/importers to supply a certain minimum pre-marketing data set (MPD) before placing a new chemical substance on the market: the test data to be generated experimentally using standard OECD testing guidelines.

From the information presented at the workshop, it was apparent that the majority of Member Countries had introduced notification schemes based on the principle of an MPD although the content of the testing package often diverged from that recommended in the Council Act. One notable exception to this general tendency was, however, the United States of America where the notification scheme for new chemicals established under the 1976 Toxic Substances Control Act (TSCA) did not, a priori, oblige manufacturers/importers to carry out testing before placing a new substance on the market. Essentially, the scheme established under TSCA required the submission of available data, often extremely limited, to the regulatory authority, in this case the Environmental Protection Agency (EPA). Faced with this paucity of experimental data, the EPA were obliged to place increasing reliance on techniques known collectively as (Quantitative) Structure Activity Relationships (Q)SAR, in order to carry out a preliminary hazard/risk assessment of notified substances: (Q)SARs are predictive methods which estimate the properties (activity) of a chemical e.g. melting point, vapour pressure, toxicity and ecotoxicity, on the basis of its structure.

One of the most important recommendations from the OECD workshop was that an attempt be made to evaluate the predictive power of the (Q)SAR, used by the EPA. It was in addition recommended that this evaluation be achieved by applying the (Q)SAR methods to chemicals for which extensive test data were already available and then comparing the properties predicted by SAR with the properties observed from experimental testing.

In the European Community, a new chemicals notification scheme came into force in 1981 in accordance with the rules laid down in Directive 79/831/EEC, being the sixth amendment to Directive 67/548/EEC on the classification, packaging and labelling of dangerous substances. The notification procedure required manufacturers/importers to submit a standardized data set (roughly similar to the OECD MPD) with experimental data being generated according to prescribed test methods (essentially equivalent to OECD test guidelines). By 1989, the EC notification scheme had been in force for over 8 years and several hundred notifications had been received. The OECD workshop therefore recommended that the predictive power of the (Q)SAR methods used by the EPA should be evaluated against the data submitted on chemicals in the context of the notification scheme established in the European Community.

The recommendations from the OECD workshop were therefore the starting point for the collaborative project between the European Community and the United States of America, which is described in this report. It must be emphasized that the scope of this project was limited to that defined by the OECD workshop namely: an evaluation of the predictive power of the (Q)SAR techniques used by the EPA in the context of the new chemicals notification scheme established under the Toxic Substances Control Act. The project is not, and was not designed to be, an evaluation of QSAR techniques in general.

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N.B. : New chemicals notification schemes in the United States of America and the European Community. In order to understand fully the design of the collaborative project, its implementation and the conclusions which can be drawn from it, it is essential to understand the details of the notification schemes as they are applied in the United States of America under the Toxic Substances Control Act and in the European Community under Directive 67/548/EEC as amended. Descriptions of the schemes are to be found in chapter 3 of this report.

## 2. Project Design

### 2.1. Competent Bodies

In the United States of America, the Agency responsible for processing the new chemicals notifications and the body responsible for the realization of this collaborative project is the Environmental Protection Agency.

In the European Community, each of the 12 Member Countries has designated national Competent Authorities responsible for the implementation of the notification scheme established under Directive 67/548/EEC as amended. The Commission of the European Communities is also involved in the implementation of the notification scheme as well as being responsible for ensuring co-ordination between the Member States. For the purposes of this project, the Commission of the European Communities was mandated by the national Competent Authorities to act as the contact point with the EPA. For the detailed realization of the project the input from the EC was co-ordinated by the Commission with advice and support from the national Competent Authorities.

Lists of the EPA and EC experts who were responsible for carrying out the detailed analyses upon which this report is based, are included as Annex 1.

### 2.2. Confidentiality

Directive 67/548/EEC, as amended, makes clear that the confidential data included in a notification dossier can only be made available to the national Competent Authorities designated as being responsible for implementing the Directive, and the European Commission. Within the national Competent Authorities and the Commission only a restricted number of staff are allowed access to this confidential information and extensive measures are taken to ensure the physical security of this information.

Given the obligations imposed under the Directive, the confidential data submitted to the European Authorities could not be made available to the EPA without the specific permission of the manufacturers/importers who had submitted the notifications in Europe. Therefore, prior to the start of the project, the national Competent Authorities in the EC Member States wrote to all notifiers asking for permission to release confidential data to the EPA for the purpose of this collaborative project. It was made clear to the notifiers that the EPA had undertaken to accord the same degree of protection to confidential data submitted under this project as they would to confidential business information submitted as part of a new chemical notification under TSCA.

A total of 107 companies responded positively to the request made by the national competent authorities. A list of these companies is attached as Annex 2 to this report. The EPA, the national Competent Authorities and the European Commission would like to thank these companies for their assistance without which this project could not have been carried out.

Confidential information, exchanged between the EPA and the European authorities was taken by hand from the notification unit located in Direction General XI of the European Commission in Brussels to the mission of the United States of America to the European Commission. From there the information was transferred by diplomatic bag to the EPA in Washington. While in the EPA the data were held in secure areas dedicated to the storage and processing of confidential business information. At the end of the project, confidential documents supplied to the EPA were destroyed.

## 2.3. How the project was organized

Discussions with EC notifiers regarding the release of confidential data to the US authorities were completed by December 1990. All together, companies gave permission for information, on a total of 175 substances to be included in the project. Chemicals were removed from the study if, for example, they were on the original TSCA inventory or had been submitted under the US notification scheme and had been accompanied by the equivalent of the MPD. This reduced the test set of chemicals to a total of 144. The various use categories of substances notified under the EC scheme were reasonably well represented in this set of 144. The dates of notification ranged from 1983 to 1990. For the US, however, the scarcity of polymers and the inclusion of pesticides and pharmaceutical intermediates represents a somewhat atypical data set of chemicals and, as such, may not have been as good a match with the US experience as could be desired.

In autumn 1991, DG XI of the European Commission communicated to the EPA the following information in relation to each of the substances selected for the study :

- IUPAC name
- CAS number (where available)
- physical form
- melting point
- use (where this was adequately described in the original dossier).

Prior to the dispatch of information, the Commission and the national competent authorities were provided by the EPA with details of the (Q)SAR methods that the EPA would use during the collaborative project.

The EPA treated this input data in exactly the same way that they would have treated data submitted under the TSCA new chemicals notification scheme, applying (Q)SARs to predict the properties of the chemical and carrying out a preliminary hazard assessment. For each substance the EPA drew up a one/two page summary of their analysis. These summaries were delivered to DG XI of the EC Commission in March 1992 and thereafter to the national competent authorities.

In April 1992, DG XI communicated the full test dossiers on each of the 144 substances to the EPA.

Between April 1992 and September 1992 the US EPA on the one hand and the EC Member States/Commission (DG XI) on the other reviewed and analysed the result of the study. Between 14-16 October 1992, a joint meeting of US and EC experts took place at the Umweltbundesamt in Berlin to discuss the results of the project. Following that meeting, this final report was prepared for onward transmission to the OECD.

## 3. Notification schemes in the European Community and in the United States

### 3.1. Essential features of the notification scheme for new chemical substances in the European Community

- **Overview/Legal basis**

The new chemicals notification scheme is established within the framework of Directive 67/548/EEC on the classification, packaging and labelling of dangerous substances. The notification scheme was in fact introduced in the 6th amendment to the basic Directive (Directive 79/831/EEC) which came into force in the EC Member States in 1981. [A copy of the sixth amendment is attached as Appendix 1].

The obligation to submit a standard notification dossier harmonised at the level of the EC falls upon any manufacturer or importer wishing to place a new substance on the market in quantities greater than 1 tonne per annum per manufacturer. [Notice that the EC scheme is a pre-marketing scheme and not premanufacture as is the case in the United States.]

A "new substance" is defined as one that is not to be found on the European Inventory of Existing Commercial Chemical Substances (EINECS). EINECS contains over 100,000 chemicals on the EC market before 18th September 1981.

Even if a chemical is new it may not need to be notified if it falls into one of the exempted product sectors e.g. pharmaceuticals, or substance classes e.g. polymers containing "old" monomers, which are specified in Articles 1 and 8 of the Directive respectively.

Notifiers are required to submit a notification dossier relating to the substance as marketed, including any impurities and additives necessary for keeping the substance stable but without separable solvent. This means that the substance or entity assessed is very rarely a pure substance and indeed some of the properties observed may be due to the impurities or additives present in the "substance". This means that the assessment is made on the entity to which man or the environment will actually be exposed rather than on the pure substance.

- **Information to be provided by the notifiers**

Notifiers must submit a notification dossier including an extensive technical dossier containing the results of the experimental testing carried out on the substance. The contents of the technical dossier are laid down in Annex VII to the Directive. This standard testing package is known as the "base set" test dossier. When the marketing levels for a substance reach 10 tonnes per annum per notification the authorities may require further testing. When marketing levels reach 100 tonnes and 1 000 tonnes per annum the notifier is required to carry out further testing. These obligatory supplementary testing packages are known as the level 1 and level 2 testing packages respectively and are laid down in Annex VIII to the Directive.

The testing methods to be used in carrying out testing of chemicals for the purpose of notification are laid down in Annex V to the Directive.

The "base set" test package is approximately equivalent to the OECD Minimum Pre Marketing Data Set (MPD) and the testing methods in Annex V are, for the majority of tests, equivalent to the corresponding OECD test guidelines. Requiring testing according to agreed standard test methods has the distinct advantage of facilitating comparison of substances.

- **How does the notification scheme work ?**

The notifier submits a notification dossier to the competent authority in the Member State where the substance is manufactured or imported. Forty five days after the authority is in receipt of a dossier which conforms to the Directive, the notifier can place the substance on the market anywhere in the European Community.

The authority receiving the notification prepares a summary dossier which is circulated through the Commission in Brussels to the other eleven Member States (a copy of the summary dossier is attached as Appendix 2).

The other Member States and the Commission can request the lead authority to make changes to the dossier or ask the notifier for further information.

The essential feature to note about the notification scheme is that it is a de-centralized one: the lead authority effectively takes the decision as to the acceptability of the notification dossier on behalf of the rest of the Community. In order for this de-centralized approach to work effectively the degree of flexibility/subjectivity which the system can tolerate is rather small: it is not one single group of people which take the decisions but 12 different national authorities each acting alone with the Commission playing the role of co-ordinator. This is one of the main reasons for the perceived rigidity in the EC notification scheme which is based upon a fixed set of information which must be supplied for each substance. This loss of flexibility is one of the costs to be paid for the benefit of having a notification scheme which has worked effectively across 12 different countries for over 10 years.

- Classification and Labelling

Directive 67/548/EEC as amended contains detailed and extensive rules for the classification and labelling of dangerous substances. Substances are classified on the basis of objective, often very precise, criteria which are laid down in Annex VI to the Directive (the version of Annex VI in force at the time of this study is included as Appendix 3). The classification criteria are in turn based upon the results of the tests carried out on the substance. The rules laid down in Annex VI also determine whether the labelling of a substance should carry a pictogram/symbol indicating certain types of danger and also whether the label should indicate certain standard phrases describing the risk of the substance, so called R-phrases, as well as certain standard phrases describing how the substance can be used safely, so called S-phrases.

In addition to determining the labelling of a substance, the classification is the starting point for the risk assessment in the European Community and also drives downstream legislation concerned with aspects of risk management, e.g. worker protection.

As can be understood from the short description given above, classification and labelling, and in particular classification, are central elements in the EC chemicals legislation. However, the criteria for classification are often extremely precise, for example, substances are classified as "very toxic" if the acute oral LD50 is less than or equal to 25 mg per kilogram but as "toxic" if the value is above 25 mg but less than or equal to 200 mg per kilogram. Classification schemes which demand such a high degree of precision to discriminate between substances allocated to one category or another obviously demand a high degree of precision in the estimates made of the chemical's properties. Experimental testing does generate precise values and even though this precision may be more apparent than real, it does provide an effective basis for building an objective classification scheme. (Q)SAR methods on the other hand usually generate less objective/precise estimates of chemical properties, and therefore do not immediately lend themselves as input data constructing classification schemes.

## 3.2. Essential features of the notification scheme for new chemical substances in the United States

- **Overview/Legal basis**

Persons who plan to manufacture or import a new chemical substance for a commercial purpose are required to provide the Environmental Protection Agency (EPA) with a premanufacture notification (PMN) at least 90 days prior to the activity. Section 5 of the Toxic Substances Control Act (TSCA) was designed to enable the Agency to review activities associated with manufacture, processing, use and disposal of any new chemical substance before it enters the market place. If necessary, EPA is empowered to take action to prevent unreasonable risks before they occur (pollution prevention at its basic level). This is accomplished by requiring premanufacture reporting. [A copy of the relevant part of the TSCA is attached as Appendix 4].

TSCA defines "new chemical substances" as chemical substances not listed on the TSCA Chemical Substance Inventory and not otherwise excluded by the regulations. The Inventory includes chemicals in commercial production between 1975 and 1979, and any chemicals reviewed in the PMN program which have subsequently been commercially produced. The Inventory currently contains over 70,000 chemical substances, of which over 7,500 substances have been added to the Inventory through the submission of notifications of commencement to manufacture (NOCs) after those substances had completed the PMN review process and were manufactured for commercial purposes.

The PMN program has been in place since 1979 and, through fiscal year 1992, has reviewed over 21,500 notices. The Agency took action to protect health and the environment from potential risks posed for over 1,800 of these new substances.

- **The PMN review process**

EPA developed the PMN review process to meet the statutory mandate of TSCA §5. Under the US Program, any person who intends to manufacture or import a new chemical substance is required to provide to EPA available data on the chemical structure, production, use, release, exposure, and health and environmental effects. However, section 5 does not require chemical companies to test their new chemical substances for potential toxic effects. Therefore, EPA's review (and 5(e) regulatory actions) are often conducted in the absence of data. The Agency relies on Structure Activity Relationships (SAR) to make predictions concerning the environmental fate and effects (health and environmental) of PMN chemicals. Each PMN proceeds through a screening process to determine whether more detailed review is required and to identify candidates for regulatory action. The Structure Activity Team (SAT), made up of a multidisciplinary group of experts, is responsible for the initial assessment of fate and effects. EPA focuses on the relatively few new chemicals of greatest concern--those which are structurally related to known toxic chemicals, and those about which little is known.

a. Initial screen. PMN notices go through a multidisciplined initial review designed to ascertain whether regulatory action on a more detailed analysis is warranted. Preliminary chemistry, Structure Activity Relationship (SAR) analysis, exposure, and environmental fate analyses are conducted.

b. Use of SAR in hazard assessment. Given the qualitative and quantitative limitations of the test data provided with PMNs (over half of all PMNs contain no test data), EPA has developed innovative approaches to characterize the potential hazards associated with new chemical substances. The major components of EPA's SAR-based approach to hazard analysis are the following:

- critical review of submitted test data, if any, on the PMN chemical;

- identification and selection of potential analogues and/or prediction of key PMN metabolites, followed by critical review of test data available on these chemicals;

- use of QSAR (Quantitative Structural Activity Relationships) methods when available and applicable; and

- the experience and judgement of scientific assessors in interpreting, weighing, and integrating the often limited information yielded by the above hazard analysis components.

The TSCA PMN reporting requirements can be compared with the European Community's (EC) "premarketing" notification requirements. As the terms indicate, premanufacture notification under TSCA is required at an earlier point in the development of a chemical than is the case for the EC's premarket notification procedure. Many of the information reporting requirements under the EC directive are similar to those in TSCA with the major difference that the EC directive requires, as a mandatory part of the notification, a specified "base set" of health, environmental, and physical chemical test data. Therefore, a minimum set of test data is available on premarket notification EC chemicals, whereas the hazard assessment of TSCA PMN chemicals often starts out with fewer or no data.

c. Cases completing their initial review are brought to the first regulatory decision meeting called "Focus". At this meeting, the results of the Initial Screen analyses are presented and considered and a decision rendered on each PMN case. The possible outcomes include: drop the case from review; hold it over for more investigation (standard review); or move directly toward a regulatory outcome for certain standard categories of chemicals. To date, the Agency has developed over 35 chemical "categories of concern" to facilitate the new chemicals review process.

d. For chemicals which are not screened out early, the standard review includes:

- Conducting a chemistry analysis,
- Identifying structurally analogous substances,
- Searching the literature for toxicity data,
- Analysing test data on the substance or analogous substances,
- Analysing potential releases to the environment,
- Estimating exposures to workers and the general population,
- Estimating potential concentrations in surface waters,
- Investigating additional uses which could significantly alter exposure.

e. Cases completing standard review are taken to the PMN Disposition Meeting for a final decision. The meeting can result in a decision to drop a case from further review, to regulate (and require controls) under section 5(e) or 5(f) (see below), or to "ban" the substance pending the receipt and evaluation of "upfront testing."

f. If a regulatory decision to impose certain controls on the manufacture, process, use, distribution, or disposal of a new substance is reached, EPA staff communicate and negotiate with the submitter. Similarly, if "upfront" testing is recommended in face of banning the new substance, this decision is also communicated to the submitter by EPA staff.

g. Notice of Commencement (NOC) of Manufacture or Import. An NOC must be submitted within 30 days of commencement of commercial production of a chemical substance which has completed the 90-day review period. The substance is then added to the TSCA Inventory.

**Regulating new chemical substances under TSCA**

**Section 5(e) and 5(f) of TSCA authorize EPA to prohibit or limit the manufacture, processing, distribution in commerce, use, and disposal of a new chemical substance if EPA makes the following determinations:**

**a. Section 5(e) findings:**

- **Available information on the substance is insufficient to permit a reasoned evaluation of its health or environmental effects; and**

- **(1) The manufacture, processing, distribution in commerce, use, or disposal of the substance may present an unreasonable risk of injury to health or the environment (referred to as a "may present" or risk-based determination); or**

- **(2) the substance will be produced in substantial quantities and (A) may reasonably be anticipated to enter the environment in substantial quantities, or (B) there may be significant or substantial human exposure (referred to as an "exposure-based" finding). An exposure-based review is triggered by an estimated threshold production volume of 100,000 kilograms per year. For those substances meeting significant or substantial human exposure criteria, chemical manufacturers may be asked to perform some or all of the following tests on their PMN substance: an Ames assay, an in vivo mouse micronucleus test, a 28-day (oral) repeat dose toxicity test and an acute oral toxicity test. PMN substances meeting the environmental release criterion may be tested for algal acute toxicity, daphnid acute toxicity, and fish acute toxicity. Additional elements of the exposure-based testing policy may include environmental fate testing and, for PMN substances having higher production volumes, developmental toxicity testing requirements.**

**b. Section 5(f) findings:**

- **There is a reasonable basis to conclude that the manufacture, processing, distribution in commerce, use, or disposal of the substance will present an unreasonable risk of injury to human health or the environment before a TSCA §6 rule can be issued to prevent the risk (referred to as a "will present" determination):**

- **A section 5(f) rule, which limits activities involving a new substance, is a section 6(b) proposed rule which is immediately effective upon proposal. A section 5(f) order prohibits all activities involving the substance. (To date, EPA has issued 3 section 5(f) rules and no section 5(f) orders, although a number of PMNs have been withdrawn from review after EPA notified the submitters that the Agency intended to ban the substances)**

**c. Practices under section 5(e):**

**To date, there have been five outcomes, depending upon the facts of the case, when EPA has made a determination under section 5(e):**

- **The company may withdraw the PMN.**

- **The company may develop toxicity information sufficient to permit a reasoned evaluation of the health or environmental effects of the substance prior to the conclusion of the review period ("upfront" or "voluntary" testing). Where exposures or releases cannot be controlled pending testing to address EPA's concerns, or the requested testing is relatively cheap and not very time-consuming, this may be the only option available to the PMN submitter short of withdrawing the PMN.**

- The company may develop and provide to EPA other information on the potential effects of the substance or its analogues, the potential exposures, or both, which if accepted by the Agency, would negate the potential unreasonable risk determination.

- The company may, together with EPA, suspend the notice review period, and negotiate and enter into a section 5(e) Consent Order. The Consent Order would permit limited manufacture, processing, distribution in commerce, use, and disposal of the substance pending the development of information. A Consent Order may contain a requirement that toxicity data be submitted to EPA when a specified volume of the chemical has been produced. This production volume level is set where EPA estimates that profits from the chemical will support the cost of testing.

- The company may refuse to withdraw the PMN, negotiate a Consent Order with EPA, and/or conduct up-front testing or develop other information. EPA would then unilaterally develop a Proposed Order, under the procedures in section 5(e), to ban manufacture or import.