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The EEC Sixth Amendment: A Guide to Risk Evaluation for Effects on the Environment

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THE EEC SIXTH AMENDMENT : A GUIDE TO RISK

EVALUATION FOR EFFECTS ON THE ENVIRONMENT.

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A. SUMMARY

The European Communities'Directive for the notification of new chemicals (Council Directive amending for the sixth time Directive 67/548/EEC, henceforward referred to as the 6th Amendment) requires a manufacturer or importer of a new substance to submit "a technical dossier supplying the information necessary for evaluating the foreseeable risks, whether immediate or delayed, which the substance may entail for man and the environment...". This report is concerned with the foreseeable risks to the environment. These are evaluated by first performing experimental studies chosen from a series specified in the 6th Amendment and then evaluating the risk from the results plus all other relevant information available.

The studies and the risk evaluations are carried out at three Levels (Base set, Level 1 and 2) according to the tonnage marketed. The evaluation of risk at each Level influences the decisions about testing at the same, or a later, Level. A decision is required, on a case by case basis, as to which studies are necessary to provide data adequate for evaluating the risks at each Level and for deciding at which point no further studies are necessary. These questions are addressed in this report in which a rationale is given, a) for the logical choice of studies to be carried out, or in some cases omitted, and b) for the evaluation of risk to the environment, at each Level. The over-riding criteria for selecting studies is that the information developed is adequate and necessary for the evaluation of risks which may arise when the substance is used in practice.

Harmonisation of the principles of risk evaluation should be sought, but it is not possible to harmonise the details because the toxicological and exposure characteristics, and their significance, will differ from chemical to chemical.

B. INTRODUCTION

In 1979 the European Communities published a Council Directive amending for the sixth time Directive 67/548/EEC relating to the classification, packaging and labelling of dangerous substances, henceforth referred to as the "6th Amendment". This amendment has been incorporated into legislation by the member states. There are some differences in the text between the 6th Amendment and the national versions of it, and in this report the English text as issued by the European Commission is used.

The 6th Amendment in Article 6.1. requires that a manufacturer or importer, before placing a new substance on the market, shall submit to the competent authority a notification including (to quote) :

"- a technical dossier supplying the information necessary for evaluating the foreseeable risks, whether immediate or delayed, which the substance may entail for man and the environment, and containing at least the information and results of the studies referred to in Annex VII, together with a detailed and full description of the studies conducted and of the methods used or a bibliographical reference to them;
- a declaration concerning the unfavourable effects of the substance in terms of the various uses envisaged;
- the proposed classification and labelling of the substance in accordance with this Directive;
- proposals for any recommended precautions relating to the safe use of the substance."

While information in the technical dossier serves to fulfil all of these requirements, this report is concerned only with "evaluating the foreseeable risks, whether immediate or delayed, which the substance may entail for.....the environment", under normal conditions of use and disposal. According to Art. 7.1 of 6th Amendment the competent authority is "responsible for receiving the information provided for in Article 6 and examining its conformity with the requirements of the Directive, and in particular - the notifier's proposed findings on any foreseeable risks which the substance may entail". Information is required at three Levels (Base set, Level 1 and Level 2) depending on the tonnage marketed, and at each Level the notifier has to evaluate the risk as a guide to the further ecotoxicological

studies required at the next Level, or to a decision that further studies are unnecessary.

The purpose of risk evaluation as outlined in this document is to identify possible areas of risk to the environment, i.e. not to prove that a substance is "safe" but rather to indicate how potentially hazardous chemicals can be used, for the purposes notified, with minimum risk. It will enable "recommended precautions relating to the safe use of the substance" (6th Amendment, Art. 6.1) to be adopted, although this aspect is outside the scope of the present document.

The information required under the 6th Amendment (see Annex VII and VIII in Appendix G.1 of this report) concerns the fate and toxicity of a chemical. Base-set information includes many parameters which are fundamental for risk evaluation. The ecotoxicological tests in Levels 1 and 2 comprise further studies on the ecotoxic effects of the substance, and the persistence/accumulation properties related to its environmental fate. From the information generated an evaluation of risk is made at each of the 3 Levels, for the tonnage and uses notified.

Base-set information (Annex VII, 6th Amendment) must be provided when the marketed volume of a new substance exceeds 1 tonne/year. Information necessary to enable a risk evaluation to be made at Level I (Annex VIII) may be requested by the authorities after being informed that the tonnage has reached 10 t/y and must be requested by them at 100 t/y. The testing necessary at this Level should preferably be discussed between the manufacturer and the competent authority. When the marketed volume reaches 1000 t/y a similar discussion of testing at Level 2 (Annex VIII) must take place.

Both annexes VII and VIII contain the sentence - "If it is not technically possible, or if it does not appear necessary to give information, the reasons shall be stated". This permits some flexibility in choosing logically which tests to carry out and in what sequence. The question therefore arises : what tests are necessary to provide data adequate for risk evaluation at each Level, and at what point can the testing be terminated ? A fixed set of obligatory tests cannot serve for the evaluation of risk for all substances. Justification has to be given when it is decided to : carry out tests at an earlier or later Level than is indicated by tonnage; carry out tests not

listed in Annex V of the Directive; omit certain tests. The overriding criteria for selecting studies are that the information developed is adequate and necessary for the evaluation of the risks which may arise when the substance is used in practice.

Harmonisation of the principles of risk evaluation should be sought so that a common approach is used by notifiers and the authorities in the various countries. Harmonisation of the risk evaluation in detail is not possible because the toxicological and environmental characteristics, and their significance, will differ from chemical to chemical. It is strongly emphasised that the somewhat detailed guidance given in this document may not apply in all cases. The notification will normally be based on an expert interpretation of which sequence of tests (within the limits of choice in the 6th Amendment) is optimum for the purpose, and how the risk evaluation is to be made, for each individual substance. In particular, water-insoluble and highly-volatile substances present problems in many of the required tests, and may need special treatment.

C. THE APPROACH TO RISK EVALUATION

1. Basis

The environmental risk of a substance is evaluated by comparing a no-effect concentration with the potential environmental concentration (PEC) of the chemical in the appropriate compartment after reasonable dispersion. This comparison is expressed as a ratio of these concentrations, allowing an estimate of the safety margin to be made specific to the tonnage, use and disposal patterns, and the location. The evaluation is based on all relevant data on effects, tonnage, use, disposal, receiving compartment and fate, available at the particular Level concerned.

Certain of the tests carried out under the 6th Amendment give information on effects for various species. Information from other tests (physical-chemical properties, stability, degradation, etc.) will usually make it possible to assess in which environmental compartment a chemical will mainly appear. It will often be possible to define scenarios taking into account the foreseen volume, use and disposal of the substance as the

basis for estimating the PEC even from the data generated at the Base-set Level.

The concept of PEC in this document is very similar to that developed by the OECD (1982). It should not be confused with the OECD concept of the Potential Environmental Distribution in which generalised mathematical models are used to estimate the PED. For risk evaluation, in the sense of the term in this document, the PED is not sufficient and the estimated PEC should be used.

Where broad scenarios for estimating PEC can be defined they should relate to the "fields of application" categories specified in section 2.1.2 of Annex VII, i.e.

i) Industries
ii) Farmers and skilled trades
iii) The public at large.

When the foreseeable uses in the above categories, and hence the corresponding environmental dispersions, are known, the most appropriate scenario or scenarios can be developed for estimating the PEC. After the substance has been placed on the market, measurements of actual environmental concentrations resulting from use may be available for estimating the PEC, and for the subsequent discussions of testing necessary at Levels 1 and 2.

It is emphasised that if the comparison of data on toxic effects with estimated exposure at the Base-set Level indicates a need to refine the risk evaluation, further information should be sought to improve the estimates of both the toxicological effects and the environmental fate.

There will undoubtedly be cases when scenarios adequate for the estimation of the PEC cannot be defined because the data on use and disposal are insufficient. In such cases it may be possible to estimate the PEC by analogy with existing chemicals for which information on environmental concentrations exists, and whose relevant characteristics are broadly similar to those of the new substance. For example, for a substance which goes mainly into surface waters a preliminary estimate of PEC can be adopted as follows. From data on the measured concentrations of industrial chemicals in surface waters it seems that after dispersion (i.e. excluding local discharge points) the

concentrations rarely reach 10 µg/l even for products of which much more than 1,000 tonnes are produced per year - see Appendix G.2. If this is accepted as a useful generalisation, then a conservative estimate of the PEC would be 1 µg/l in the range 1 to 100 tonne/year, and 10 µg/l in the range 100-1000 tonne/year. At above 1000 tonnes/year (Level 2) it is more likely that an adequate scenario can be defined because more information is available, and a more direct estimate of PEC may be possible.

Thus, either by calculation, by analogy with existing chemicals, or from actual field measurements, the PEC can be estimated for the relevant use, compartment and tonnage.

At each Level, for the various toxic effects which have been studied the no-effect-level or LC_{50} and the estimated PEC are compared to evaluate the risk in the relevant environmental compartment, and a judgement is then made whether the ratio of these indicates :

a) that the risk at this Level is not significant or can be adequately controlled by appropriate measures, and that no further testing or other action is necessary ;
   or
b) that the risk is not adequately defined, and that further information is necessary to define it more accurately.

2. Some Useful Generalisations.
   For making rational decisions on which tests are necessary to permit the evaluation of risk at each Level, the following generalisations will prove to be useful.

2.1. Relationship of acute to sub-lethal and chronic effects in aquatic organisms. In the absence of information about chronic toxicity,a ratio of 100 between an LC_{50} and the environmental concentration could be taken as guidance indicating negligible risk, for the following reason. Sprague (1971) and Maki (1979) found that for the great majority of chemicals which they tested, sub-lethal and chronic effects on aquatic species are not likely to occur at concentrations below 1% of the acute LC_{50} (Base-set tests on fish and Daphnia). Thus, when the PEC is below 1% of the LC_{50} for both fish and Daphnia it can be considered as being below the threshold concentration for sub-lethal or chronic effects, and

testing for such effects need not normally be performed. This may not apply if the curve of LC_{50} vs time in the LC_{50} test has not reached a plateau or if there is evidence that bioaccumulation may be significant.

2.2. Degradability. Evidence of biotic or abiotic degradability from the Base-set tests indicates routes by which a chemical can be removed from the environment. As a working hypothesis at the Base-set Level it can be assumed that for a chemical which is readily biodegradable in any of the Base-set tests, 90% will disappear rapidly from the aqueous environment. Conversely, for a chemical which is not readily biodegradable, zero removal from water should be assumed unless there is evidence of degradation from tests at Levels 1 or 2, or of removal by other routes (eg. volatilisation or adsorption).

In estimating the PEC of a substance which reaches the soil it is useful to note that biodegradation in soil is usually at least as rapid as in surface waters because of the greater variety and density of micro-organisms in fertile soil.

It is emphasised that substances of low or zero degradability do not necessarily represent a hazard to the environment.

2.3. Bioaccumulation. Evidence that a substance may bioaccumulate, especially in a food-chain organism (such that organisms higher in the chain may be exposed to toxic levels), will influence the decisions involved in risk evaluation.

It is now widely-accepted that deductions about the bioaccumulation of, in particular, non-ionised substances in aquatic species can be made from the partition coefficient of a chemical between n-octanol and water (Pow; Base-set measurement). If the Pow is below 1000 the risk of bioaccumulation in aquatic species is low (Bioconcentration Factor below 100) since the normal route of bioaccumulation is by migration from the external environment into lipids in the organism. If the Pow is above 1000 the possibility of significant bioaccumulation must be taken into account.

According to the OECD Test Guideline 305A, page 6, a bioaccumulation study is not justified for substances whose water-solubility exceeds 2g/l, irrespective of the results of any previous biodegradation test. Substances which are soluble in water to this extent are not considered likely to be sufficiently soluble in lipids to bioaccumulate.

2.4. Toxicity to higher plants. Information useful for deciding whether to test a chemical for effects on a higher plant has been provided by Kenaga(1981). He collected data on 131,596 varied chemicals regarding their lethality to 5 species of terrestrial plant seeds (pre-emergence or germination effects) or seedlings. Only 0.17% of these chemicals killed the seeds at a concentration of 1 ppm or lower. This strongly suggests that it is unnecessary to carry out the higher plant test if the concentration in soil is unlikely to exceed 1 ppm (1 mg/kg of soil).

D. RATIONALE FOR TESTING AND RISK EVALUATION AT BASE-SET LEVEL.

The Base-set requirements are given in the attached Annex VII of the 6th Amendment.

1. Physical-chemical Properties

The Directive requires that the measurements be carried out on the substance as marketed. This should always be so for the biological tests. However, when impurities or additives (including formulation adjuvants) required for the purpose of placing an acceptable product on the market would so alter the result of a physical-chemical measurement as to make interpretation difficult, it may be preferable to test the purified compound. If it is not possible to isolate the purified compound, the test should be omitted. When a test is carried out on a material other than the substance as marketed, the notifier should state what material was tested and give the reasons for his choice and, where necessary, its implications.

Data on certain physical-chemical properties are used to identify the substance. Other physical-chemical properties, combined with information on use and disposal, are used to estimate the environmental fate and potential environmental concentration. Vapour pressure, solubility in

water, and partition coefficient will (together with information on other factors) indicate the probable distribution of the substance between air, water, soil or sediments. The octanol-water partition coefficient is a guide to bioaccumulation potential, in particular for non-ionised compounds (see section C.2.3. above).

Most of the measurements of physical-chemical properties in solution depend on the availability of a sensitive analytical method. The sensitivity need not be greater than the level of accuracy needed for interpreting the results of each measurement. In view of the uncertainties in compartmentalisation estimates or models, high accuracy in measuring the physical-chemical properties related to such estimates is not necessary. Similarly, physical-chemical parameters required solely for assessing ecotoxicological effects need be measured only with the accuracy adequate for such assessments.

2. Degradation Tests

The main requirement in the Base-set is for a measure of ready biodegradibility, over 28 days, by any of the methods listed in Annex V of the 6th Amendment. If the compound is readily biodegradable in any of these stringent tests it can be assumed to degrade readily under aerobic environmental conditions. An even simpler test, the 5-day BOD, can give some indication of biodegradation, but only few chemicals would biodegrade substantially in the short time available. Even if the compound is not readily biodegradable in the above tests it cannot automatically be considered as non-biodegradable in the environment, and, where appropriate, further testing by the methods in Levels 1 and 2 may establish its biodegradability.

Many compounds, because of their physical state and/or low solubility, will not readily degrade under the above conditions, while others will not be readily degraded for reasons of chemical structure. Although such resistance to breakdown must be taken as indicating potential persistence, it will not be automatically necessary to carry out more vigorous or prolonged testing at this Level. For example, materials which by their function are required to resist biodeterioration in service could be declared to be non-biodegradable without testing at any Level.

Information on abiotic degradation is required at this Level. Data on susceptibility to hydrolysis seem unnecessary for substances which have already proved to be biodegradable. The determination of photodegradability in the atmosphere is not justifiable at the very low tonnage involved at the Base-set Level because even for persistent substances the PEC, after dispersion of the product in air, will be negligible at up to 100 t/y.

3. Acute Toxicity to Aquatic Organisms

Data on LC_{50} (the concentration which kills 50% of the test organisms, calculated on a statistical basis) for a fish species and Daphnia magna is required in the Base-set. These organisms were chosen to represent species in the aquatic environment. Daphnia stands between Algae and fish in the food chain. In most cases the curve obtained by plotting toxic concentration to fish against time will reach a plateau value by 96 hours (the specified test period is 48 hours, optionally extended to 96 hours). Failure to do so may indicate a need for further testing, normally at Level 1.

These LC_{50} determinations need not be carried out when the chemical will not reach the aquatic environment, for example in the case of a very volatile, water-insoluble substance.

4. Risk Evaluation

From Base-set information a preliminary prediction can be made of the environmental compartment(s) in which the substance will mainly appear. A comparison of the PEC (related to the appropriate use scenario) with the information on degradability, and toxicity to fish and Daphnia, will often enable a first risk evaluation to be made for the substance in surface waters. It may also be possible to exclude the likelihood of risk in other compartments if it is clear that the substance is not likely to reach them in significant amounts.

For some substances the risk evaluation made at the Base-set Level may prove to be adequate for the higher Levels also. When this is not the case, risk evaluation at the Base-set Level assists in selecting tests which are logically justified and necessary when Levels 1 and 2 are reached, so that the evaluation can be improved.

E. RATIONALE FOR TESTING AND RISK EVALUATION AT LEVELS 1 AND 2

Levels 1 and 2 include further studies on the potential ecotoxic effects of the substance, and on its persistence/accumulation properties. Such studies enable the data on toxicity and fate generated in the Base-set to be refined so that the risk evaluation can be correspondingly improved. The tests on Algae, Daphnia, fish, a higher plant, and earthworms yield data on toxicity, while those on biodegradation, accumulation and mobility give information relevant to the estimation of the PEC.

1. Level 1

1.1. Algae test. This test involves measuring the effect of a substance on the growth of a unicellular Algae species, selected because it is common and convenient to use in the laboratory and is a primary food source for certain aquatic organisms. The results, expressed as an EC_{50} (the concentration of the chemical causing a 50% inhibition of growth) and a highest-tested no-effect level, can be compared with the PEC for risk evaluation.

When the LC_{50} for Daphnia and fish are more than 100 times the PEC there may be no need to perform the test on Algae. Kenaga and Moolenaar (1979) compared the acute toxicity of many thousands of chemicals, of various structures, towards a number of fish species, Daphnia magna and Alga chlorella. The fish and Daphnia proved, in most cases, to be at least as sensitive as Algae chlorella in indicating toxic effects. The results showed that only rarely would a substance with an adequate safety margin for fish and Daphnia be acutely toxic to Algae chlorella.

On the contrary, if a chemical seems likely to be stable in water and has an acute toxicity to fish or Daphnia high enough to raise concern when compared with the PEC at 10 t/y, it may be of value to carry out the Algae test at this stage in Level 1, so as to gain further information on its toxicity to aquatic species.

1.2. Prolonged (21-day) toxicity to Daphnia magna. This is a convenient aquatic organism for studying the potential effect of chemicals on reproduction, a chronic effect. Because (see C.2.1) the chronic no-effect concentration for aquatic organisms is generally above 1% of

the acute LC_{50} , it is not necessary to carry out the prolonged Daphnia test on chemicals for which the PEC is below one-hundredth of the LC_{50} to Daphnia.

Should the Base-set results show that a chemical is likely to be stable in water, and the comparison of its acute toxicity to Daphnia with the PEC causes concern (particularly if the substance has the potential for significant bioaccumulation), it may be of value to get information on chronic toxicity by carrying out the prolonged Daphnia test at 10 tonnes/year in Level 1, instead of at the 100 tonnes/year stage.

1.3. Higher plant test. This test gives information on the effect of the chemical, expressed as an EC_{50}, on the germination and growth of a higher plant. It is not normally necessary at Levels 1 or 2 for chemicals shown to be readily biodegradable in water (see comment on biodegradation in soil, C.2.2) or not likely to reach the soil in concentrations of above 1mg/kg (see C.2.4).

1.4. Earthworm Test. This test gives information on the effect of a chemical on earthworms, a particularly important soil macro-organism. The result is expressed as an LC_{50}. An earthworm test would normally be necessary only for chemicals which are likely to reach the soil in significant concentrations, eg. via application of sewage sludge or by other direct means.

1.5. Prolonged (14-day) fish toxicity test. When no plateau has been reached in the curve of concentration against time in the LC_{50} (Base-set) test on fish, the prolonged study should be carried out (see D.3). It is not normally necessary to perform it if a plateau has been reached in the Base-set test and the PEC is below one-hundredth of the LC_{50} for fish.

If the Base-set results indicate that the substance is likely to be stable in water, and a comparison of its acute toxicity to fish with the PEC causes concern (particularly if the substance has the potential for significant bioaccumulation) it may be valuable to obtain information on chronic toxicity by carrying out the prolonged test at 10 t/y instead of 100 t/y at Level 1.