RSC | Advancing the Chemical Sciences

Environment, Health and Safety Committee Note on: EXPLORING THE PRACTICAL ASPECTS OF CHEMICAL SUBSTITUTION

ABSTRACT

Authorisation provides a regulatory context for substitution. Substitution is a complex process and should be based on risk. Substitution should be goal-orientated rather than prescriptive. Comparative risk assessment provides data for substitution decisions. Stakeholders should be consulted when developing substitution criteria. Risk profiles should be developed for candidate substitutes. Experts should summarise the risk profiles of candidate substitutes for evaluation according to agreed criteria. Selection of substitutes for specific uses will require value judgements based on comparative risk evaluation and stakeholder input.

1. INTRODUCTION

Ideally society would like industry to develop chemical substances that can deliver a desired property or effect without negative side-effects e.g. flame retardant clothes are desirable but not flame retardant chemicals with bio-accumulative properties. In reality, risk has to be the main consideration as, to some extent, all process and chemicals are hazardous. The REACH (Registration, Evaluation and Authorisation of Chemicals) Regulation requires that chemicals be 'Authorised' for specified uses in those cases where the perceived benefit (either as with human medicines, to the individual, or as with biocides, plant protection products, food additives, etc. to society as a whole) is disproportionate in comparison with the risk. The purpose of this paper is to consider the 'how' rather than the 'why' of substitution, and to propose some practical approaches that could lead to sustainable and improved human and environmental health.

The substitution principle has wide application, both within and outside REACH. However, substitution may also be necessary when manufacturers cease to produce a chemical, cease to support its use in a particular type of preparation, or when downstream users or the public seek the elimination of a particular substance from certain types of preparation and/or article. Supply chains are not necessarily simple supplier/user relationships, and in the type of complex supply chain illustrated in Figure 1, which is not atypical of that seen in the lubricant industry, removal of a chemical can potentially have a significant impact further down the chain.

Substitution may occur at any point in the manufacturing chain. Substitution after development poses different challenges to substitution (avoidance) during development. The buying power of informed users/consumers and suppliers is also an effective mechanism for driving substitution.

2. SUBSTITUTION AS A GENERAL DUTY

Recital (or 'whereas') 73 identifies that whenever a substance is dangerous (poses an unacceptable risk) to human health or the environment its continued use should depend on an evaluation of alternatives and a socio-economic justification. Compulsory, structured consideration of substitution is only undertaken for substances of very high concern that are subject to 'Authorisation' (recital 74).

3. AUTHORISATION AND SUBSTITUTION

The 'Authorisation' process is essentially a risk management process. Substances enter the Authorisation process on grounds of hazard. Hazard refers to the intrinsic adverse or harmful property of a substance e.g. flammability, toxicity, corrosivity. Risk is the likelihood that the intrinsic hazard will cause harm. Risk is a function of

This Note was produced by a Working Party of the Environment, Health and Safety Committee [EHSC] of the Royal Society of Chemistry.

The Society is a registered Charity. Its Royal Charter obliges it to serve the public interest by acting in an independent advisory capacity. In order to meet this obligation the members of the EHSC are drawn from a wide range of backgrounds and serve on the committee as individual experts and not as representatives of their employer.

The EHSC welcomes comments on this Note. Please send them to the Committee Secretary:

Health, Safety and Environment Committee
Royal Society of Chemistry
Burlington House
Piccadilly
London
W1J 0BA

Tel: +44 (0) 207 440 3337
Fax: +44 (0) 207 437 8883
Email: ehsc@rsc.org

EHSC Notes are also available on the Society's web site at www.rsc.org

EHSC Notes are updated from time to time and details of the most up to date versions can be found on the Society's website www.rsc.org

17 April 2007

hazard and exposure. Once the likely exposure to the hazard is examined it may be that, for one or more specified uses, control is such that the risks are deemed 'broadly acceptable'. This is the circumstance where the substance can be authorised without further consideration.

The aim of Authorisation (Article 55) is to ensure the good functioning of the internal market while assuring that the risks from substances of very high concern are properly controlled and that these substances are progressively replaced by suitable alternative substances or technologies where these are economically and technically viable. To this end all manufacturers, importers and downstream users applying for authorisations are required to analyse the availability of alternatives and consider their risks, and the technical and economic feasibility of substitution.

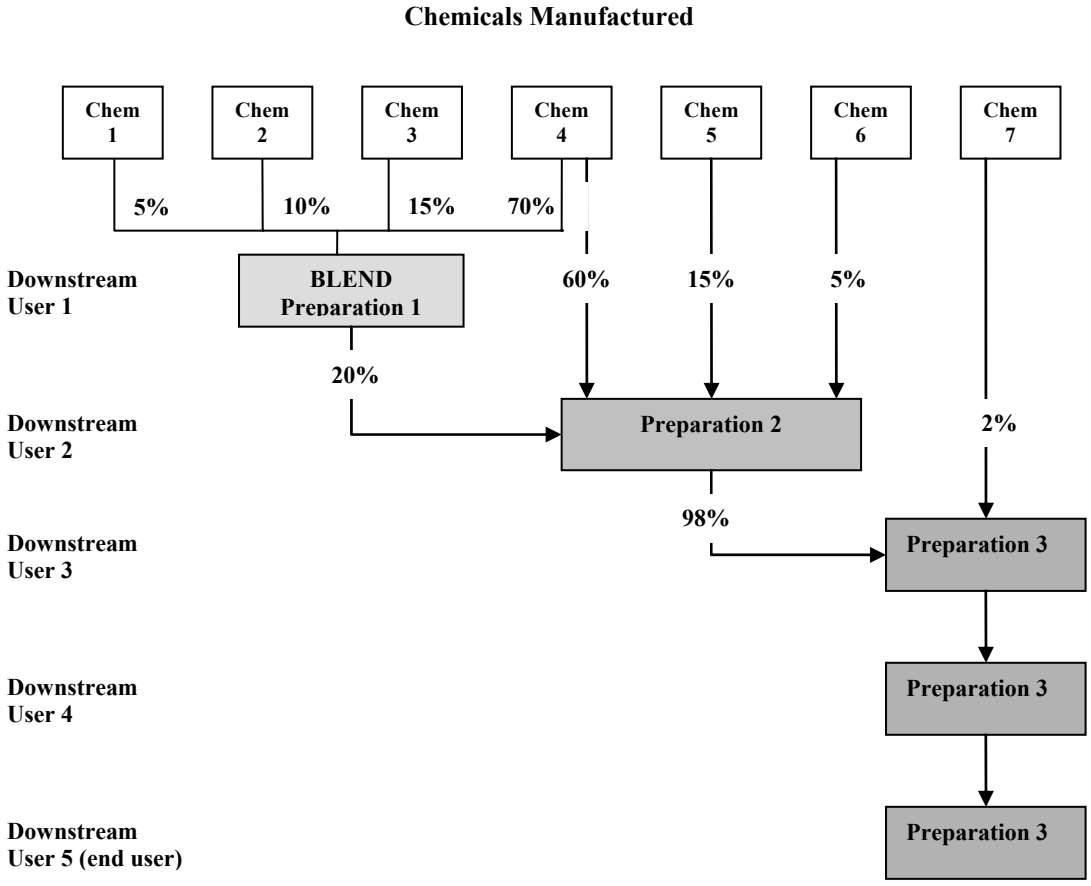

Figure1. Example of a manufacturing process

Substitution is at the heart of the proposed REACH Authorisation process for the control of chemicals in the EU. Applications for authorisations must be made to the Agency (Article 62). An application for authorisation must include an analysis of the alternatives (Article 62(4)(e) and(f)) considering their risks and the technical and economic feasibility of substitution and include, if appropriate, information about any relevant research and development activities by the applicant. Where the analysis shows that suitable alternatives are available, it must include a substitution plan incorporating including a timetable for proposed actions by the applicant.

Where exposure to the original substance can be adequately controlled and the exposure reduced to a 'safe' level (a 'broadly acceptable risk) this will be the requirement for Authorisation (Article 60(2)). A socio-economic justification is not required. Where exposure to the original substance cannot be controlled to 'broadly acceptable' levels of risk, then further risk/benefit evaluation is needed. If society has a need for the chemical/use and risks from exposure are not unacceptably high, they can be deemed 'tolerable' on socio-economic considerations (Article 60(4)).

In terms of Article 60, the Commission shall be responsible for taking decisions on applications for authorisations. Where adequate control cannot be achieved, an Authorisation may only be granted if it is shown that socio-economic benefits outweigh the risk to human health or the environment arising from the use of the substance and if there are no suitable alternative substances or technologies. All authorisations are subject to periodic review (Article 60(8)).

When assessing whether suitable alternative substances or technologies are available, all relevant aspects shall be taken into account by the Commission, including:

a) whether the transfer to alternatives would result in reduced overall risks to human health and the environment, taking into account the appropriateness and effectiveness of risk management measures;
b) the technical and economic feasibility of alternatives for the applicant.

The socio-economic justification for the continued use of a chemical substance can therefore be made if available substitute chemicals also exhibit a number of hazardous properties that lead to risks which are deemed worse than the original. In such cases REACH regulation makes provision for 'Authorising' some potentially hazardous chemicals for specific uses, even though the risks will not be 'broadly acceptable' and then only for a limited period of time.

But what constitutes an acceptable risk? The almost non toxic and non flammable CFCs were introduced to replace refrigerants that were either very toxic to humans, such as ammonia, or were extremely flammable such as propane. When this substitution took place the impact of CFCs on the ozone layer was unknown. However when this effect was discovered, the older refrigerants were reintroduced with a very significant increase in risk to the population. This highlights the need for clear Authorisation and substitution requirements. Without clear Authorisation requirements, legal certainty and market rights can't be established. Furthermore the willingness of industry to develop business opportunities or encourage continuous investment in innovation could be eroded.

The Substitution Principle is frequently expressed as 'chemicals should be substituted where a *safer alternative* exists' – this is problematic from a practical point of view. As a minimum both the word 'safer' and 'alternative' need clear definition. In the context of substitution a 'safer' substance is one that can be shown to have a substantially lower risk overall than the one to which it is being compared. An 'alternative' substance should be capable of providing a level of performance that is acceptable to the regulator, user, (and consumer if relevant) at a cost that is not prohibitive and whose supply is adequately assured. Substitution should seek to achieve an equivalent or greater functionality via technological or organisational measures. Substitution by an alternative substance should also not lead to any materially important reduction in sustainability.

4. SUBSTITUTION AND RISK REDUCTION

Substitution is not a simple process since it is necessary to ensure that the overall risk is reduced, ideally to a 'broadly acceptable' level of risk – a 'safe' level of exposure - and that a decrease in one risk is not overshadowed by the increase in another. In many cases, substituting one chemical by another can make an important contribution to producing a lower overall risk, ideally to 'broadly acceptable' levels. However, it is important to note that risk is not eliminated in this process.

Substitution is a practical outcome of comparative risk assessment and evaluation. Comparative risk evaluation aims to optimise the choice of substances for a particular use, taking into account potential risks to health, wildlife and the environment and the benefits to society as a whole.

Comparative risk evaluation poses major scientific challenges not least of which are the choices of what to compare and the decisions about what level of risk is the maximum tolerable and what level of risk is broadly acceptable. Although it may not be possible, due to time and resource constraints, to conduct a complete comparative risk assessment of all the chemical substances used for a specific purpose, comparative risk evaluation should still aim to establish:

1. The need for a particular chemical substance;
2. The availability of alternative substances that can produce the required effect;
3. The risks to humans and the environment of alternative chemical substances grouped on the basis of required use/effect;
4. The efficacy (benefits) of alternatives, that can deliver the required effect;
5. The socio-economic impact of proposed substitutions with the group of alternatives that can deliver the required effect.

Ideally, 'life cycle analysis' is required for the particular use in question. Chemicals for substitution should be considered on a case-by-case basis as each will have its own unique properties and exposure patterns. The circumstances of use of a chemical should provide information on possible problems with regard to that use. It is important to recognise that all substances possess a range of hazards, such as toxicity, flammability, corrosivity etc. and that each hazard will vary from one substance to another in terms of its magnitude and probability of causing harm to humans, animals and the environment. If however comparison of chemical substances were to be based on hazard alone, it would not be possible to allow for the differences in exposure that will occur through differences in usage patterns. For example, a particular chemical substance with a lower intrinsic hazard may need to be used in greater quantities or at higher concentrations than a chemical substance with a higher intrinsic hazard that would be more effective at lower concentrations.

The aim of comparative risk evaluation is to facilitate the development of rankings that place the 'risk profiles' of chemical substances, according to their intended uses, on an ordered scale of reducing overall risk. This is still an area in which methodologies are being developed. Comparison of chemical substances with similar use patterns is a useful tool in risk reduction. If the area of use and mode of application is similar for chemical substances then the exposure conditions can normally be assumed to be the same. Under such circumstances assessors and regulators can essentially base comparative evaluations on the hazard attributes of the chemical substances being compared.

Ranking risks requires information about the hazards of concern and judgements about their likely effects and impacts. Effective substitution of a 'problem' chemical by an alternative requires an 'adequate' set of data for the alternative. This may seem obvious, but is often overlooked with materials being substituted to remove one problem without recognising that different problems may arise as a consequence. For example ionic liquids are universally recognised as 'green' alternatives to organic solvents, however the data on ecotoxicological impact and environmental fate data for these materials is often inadequate to allow a realistic environmental risk assessment to be undertaken. There is experimental evidence that some ionic liquids are highly toxic to aquatic life and also very persistent in the environment. In the case of the REACH authorisation process, chemicals that have entered the process can be deemed to have an 'adequate' set of data on hazard and exposure, but this cannot be assumed for currently low-tonnage non authorisable chemicals.

Materials, products and chemical processes cannot be considered in isolation. In the real world chemicals exist in the context of a life cycle of activities in which people, animals and the environment may be exposed. Whether or not substitution is justified depends upon the relative acceptability of each of those risks as they are affected by such substitution. For example materials to which exposure in use offers little risk to human health may still pose considerable risks to the environment and vice-versa. Thus returning to the example of CFCs, the decision to ban their use was a good example of risk based substitution. If there had been foolproof ways of preventing their escape to the environment then it might have been better not to replace them: the alternative materials though posing less risk to the ozone layer are often more dangerous (e.g. flammable) or toxic to man. However given the impracticality of preventing CFC escape to the atmosphere, the risk they posed to the ozone layer was judged less acceptable compared with the risks to human health from their replacements. Therefore CFCs were withdrawn from use.

It is clear from this example that risk based substitution may not always be simple. It involves weighing up and comparing different hazards and their magnitudes. It also requires value judgments about the acceptability of different risks to different targets, such as judging that the risk to the ozone layer from CFCs was more important than the risk to human health from the materials that replaced them. Simultaneously ranking health, safety and environmental risks requires the participants to make difficult trade-offs among a larger and more diverse set of relevant properties of chemical substances. Cognitive constraints make it difficult for us to choose among several options which can be described in terms of several attributes that vary in terms of the nature of their effect, magnitude and timing. In order to develop a pragmatic approach to making these complex decisions, ways need to be found to simplify the decision process. This needs to be done in a way that will allow complex trade-offs among non-commensurate attributes to be made. Another point to consider is that the simpler the system the more likely it is to be implemented and actually achieve its objectives.

5. COMPARATIVE RISK EVALUATION

The key objective of comparative risk evaluation is to identify alternative chemical substances that could be substituted for existing chemical substances with similar uses where the proposed substitute presents a significantly reduced level of overall risk. Comparative risk assessment could be used to identify chemical substances for substitution in the following way:

Step 1: Identify the substances to be compared

This step involves the identification of a group of chemical substances (with a common use e.g. flame retardants) capable of delivering the desired effect, that are to be considered as possible substitutes. Qualitative judgments are then made about the likely impact on human health and the environment of each chemical substance in turn. For example a particular substance may be responsible for a number of health effects. These effects are called 'end points' and may encompass a wide variety of conditions including cancer, reproductive abnormalities, developmental disorders, central nervous system symptoms, trauma, infections, and rashes.
The identification of the group of candidate chemical substances for substitution is usually followed by an exposure assessment. This involves a description of the sequence of events through which exposure to a risk agent could occur and a determination of the extent of adverse effects likely to result from given levels of exposure to risk agents. Though this step only consists of the qualitative determination of causation based on the weight of the available evidence, it should lead to a conclusion of whether or not an adverse health or environmental effect exists as a result of a the presence of a particular chemical substance.

Step 2: Specify the key impacts to be considered

Once a list of chemical substances from which a substitute could be chosen has been compiled based on the exposure assessment the next stage of the process should seek to clarify and quantify (where possible) the 'risk profiles' of substitution candidate chemical substances by determining the expected impact caused by a range of likely exposures.

Normally a series of toxic and environmental end points are assessed when examining the risks posed by individual substances. These end points are set out in Technical Guidance Documents such as that for new and existing substances and biocides. It is anticipated that an updated version of this document will be produced for REACH. The process adopted is essentially that described in the International Programme on Chemical Safety - Environmental Health Criteria documents 170 and 210 (World Health Organisation, Geneva).

In the 'Authorisation' process a limited range of effects (the PBT (persistent, bio-accumulative, toxic) and vPvB (very persistent, very bio-accumulative) end points) are considered initially when identifying the 'key impacts' for a series of chemicals and uses. The 'key impacts' are, in effect, the PBT, vPvB and endocrine disruptor end points that caused the index substance to enter Authorisation, and are the impacts for which comparative data are sought. Occasionally an additional 'key impact' may have to be considered – for example when dealing with substitutes that are acutely very toxic by their likely route of exposure, and hence are unacceptable as substitutes.

For many end points the 'derived no effect level' (DNEL) was sought in the chemicals safety assessment. This DNEL includes uncertainty factors and therefore combines risk assessment (the technical process) with a standardised first approximation at a risk evaluation (the process involving societal judgements as well as technical considerations (Illing 1999; 2006)). Thus, for the purposes of the Authorisation process, a pure risk assessment statement, the OECD 'margin of exposure' is required, not the DNEL. The 'margin of exposure' is the ratio between the 'no observed adverse effect level' (NOAEL) for the critical effect and the theoretical, predicted or estimated exposure dose. The judgement concerning whether the 'margin of exposure' is adequate is a part of the risk evaluation. The term 'margin of exposure' is preferred in this document to 'margin of safety' as the OECD gives two different definitions for 'margin of safety'.

In seeking to examine a series of substances, absolute numbers for the 'margin of exposure' for a specific key impact can then be compared by setting them against a reference value (the substance being subjected to Authorisation). Alternatively, if the data permit, comparison may be undertaken without determining absolute numbers. In the cases of persistence and bioavailability the presence of the material in the environment is the problem. In this case, presumably, the 'margin of exposure' would be determined by taking the numerical value for the parameter in question, comparing it with the criterion value for that parameter, and then setting that number against the actual exposure value (e.g. obtaining the 'predicted exposure concentration' (PEC)/ 'predicted no effect concentration' (PNEC) ratio). The Technical Guidance Document (TGD) methods should be applied in a comparative mode.

At present there is a need to deal with the question of potency when dealing with carcinogens; the current classification system deals with carcinogens in terms of quality of evidence, not in terms of potency. The 'margin of exposure' approach is applicable to non-genotoxic carcinogens, but, for genotoxic carcinogens, the UK principle hitherto has been to jump immediately to risk management and to propose avoidance of exposure to the general public where possible and otherwise to reduce exposure 'as low as is reasonably practicable'. Comparative risk evaluation for genotoxic carcinogenesis (which may be required for workplace operator exposure) will require that a comparative risk evaluation is conducted, so the UK Committee on Carcinogenicity will have to provide advice to the UK Government on how to undertake the associated risk assessment.
Within a 'key impact' it should be possible to rank a series of chemicals on the basis of their 'margin of exposure' (to the NOAEL). If the 'margin of exposure' is deemed insufficient, it may also be necessary to deal with the question of dose-response and hence the relationship between the maximum level that could be deemed 'tolerable' and the theoretical, predicted or determined exposure. It should be possible to comment upon the quality of the exposure data available for the particular use for both the substance subject to authorisation and the alternatives. There may be inequalities in the quality of evidence concerning hazard for the alternatives that should be commented upon – for example, carcinogenicity and reproductive toxicity data may not be available for particular alternatives, if they are currently low tonnage chemicals not subject to authorisation or chemicals not placed on the market.

Risk ranking also requires consistent choices regarding how the attributes of chemical substances should be grouped; unfortunately there are no objective criteria for determining the best method to do this for ranking purposes. Perhaps the best approach is to define the risks in a manner that is most useful to stakeholders.

Every substance has its own hazard profile and although it is possible to rank substances in order of their toxicity to man or their global warming potential it is <u>not</u> possible to rank substances in order of generic 'hazard' in order to select a 'safer' alternative. Consequently, replacing one substance by another in order to reduce one specific hazard may increase one or more different hazards. The decision maker therefore needs to balance the risks posed by these independent hazards in order to determine the optimum substitute material. A simplified example of this is presented in Table 1. However, it should be noted the table only contains broad headings for areas of 'key effects', not individual 'key effects'.

Table 1. Chemical Substances Ranked by Hazardous Property

Decreasing>	***TOXICITY***	***ECOTOXICITY***	***VOLATILITY***
	Dichloromethane	**Monochlorobenzene**	**Dichloromethane**
	Trichloromethane	**Trichloromethane**	**Acetone**
	Monochlorobenzene	**Toluene**	**Trichloromethane**
	Toluene	**Dichloromethane**	**Toluene**
	Acetone	**Acetone**	**Monochlorobenzene**

Step 3: Describe the impacts

Risk profiles detailing the type and scope of risks for each candidate substitute chemical substance should be summarised, according to agreed criteria, by an expert group equivalent to the UK Advisory Committee on Hazardous Substances. This is the comparative risk assessment. These profiles should then be considered by a (primarily) stakeholder group with input from interested parties, i.e. the stakeholders take part in a risk evaluation. Ideally output of the first stage could be a matrix of alternative substances scored against the same set of criteria. This would serve to facilitate the comparison of alternative chemical substance. The expert group should also identify and explain all uncertainties and assumptions inherent in the information. Concerns that can not be adequately described in terms of summary criteria should be made explicit so that they can be factored into the risk evaluation process and subsequent follow through. This should involve a consideration of socio-economic matters and any other relevant considerations.

Socio-economic considerations include:

1. Availability of effective alternatives nationally and globally
2. Impact of loss of economic goods and services if substance withdrawn
3. Effectiveness of reformulated products for specific uses
4. Costs of reformulating products that contain active substances

Step 4: Ranking the alternatives

A key question that needs to be asked before 'choosing' between the best alternative among negative impacts of different chemical candidates for substitution is 'Do we need the chemical for this product or would society be better off without it?' If the answer to this question is 'yes', then there is a need to rank alternatives. However, one alternative may not be appropriate in all circumstances, and, as with medicines, it may be necessary to authorise several alternatives, all of which meet appropriate criteria.

To date it appears that the main driver in making substitution decisions has been human health. Concerns for the health and safety of the workforce have resulted in the 'substitution principle' being built into occupational health and safety guidelines. This view that human health appears to be more important than the environment is supported for example by recent decisions to re-introduce DDT for malaria control.

Although various attempts to produce ranking scores have been made, none have been successfully adopted. This is because these systems have been trying to impose a technical process on what is properly a societal judgement.

Where possible, the process of weighing dissimilar risks has to be based on scientific evidence. This should be based on risk profiles of the list of chemical alternatives with a particular outcome in mind i.e. desired effect (optimum outcome at with the lowest impact). Stakeholders should first individually rate and rank the impacts of each end effect for each chemical substance making use of factors such as: severity of effect (irreversibility); probability of effect (use/exposure); groups affected (vulnerable groups, the young and the old); the affected environment (aquatic, terrestrial and atmospheric); sustainability (and hence life cycle analysis); and societal attitudes to different classes of risks ('voluntary'/'involuntary', 'dread', etc.).

It is likely that each group of stakeholders will judge some risks and benefits to be more important than others e.g. flammability vs. damage to the ozone layer. Summary sheets should be used to record individual stakeholder rankings of each chemical substance for the common desired outcome. Individual stakeholders should then seek to develop group rankings, for chemical substances in discussion with other stakeholders. Although consensus is desirable it is not always possible or essential. The outcome of this process could produce a majority view as to which chemical substance is the preferred either for use directly or for incorporation into products based on achieving the desired effect at the lowest impact.

Assuming that it is possible to identify one or a number of substitutes which is, or are, on balance, 'safer' than the currently used material, it would be inappropriate to proceed without examining the sustainability impacts of making such a substitution. A 'safer' chemical may be used in larger amounts, require more energy or water to be used and/or may generate more waste. For example the transistors and silicon chips that began to replace the thermionic valve from the 1960's onwards contain semi-conductor materials that are Persistent, Toxic and Bioaccumulative (PBTs) but they utilise only a fraction of the resources and energy. The decision maker must therefore again balance the safety of the substitute against any potentially negative sustainability impacts in order to determine the optimum substitute material.

Where the differences in terms of the gains by substituting one chemical substance for another (for a specific use) are clear, then substitution should be required. Difficulties arise in those situations where the comparative risk assessment process highlights differences between two candidate replacement substances in terms of their predicted impacts. In such cases, where no satisfactory methods exist to make a reliable comparison possible, substitution should not be required. For example a chemical substance with a higher risk to aquatic organisms, would not normally be substituted by another with a lower risk in that area but a higher risk in a different area e.g. to birds. In such cases the outcome of the

process would be information that could be used to aid users make choices about which chemical substance to use in different situations, according to their risk profiles. Such information could also be incorporated into the labelling of products.

Under REACH the final substitution decision will be a value judgement on the balance of risk and benefit made by the European Chemicals Agency on behalf of society, taking stakeholder views into account.

REFERENCES

Illing, H P A, 'Are societal judgements being incorporated into the uncertainty factors used in toxicological risk assessment', Regulatory Toxicology and Pharmacology 29, 300-308, 1999.

Illing, P, 'General overview of the safety evaluation of chemicals' in R E Hester and R M Harrison 'Alternatives to animal testing' Issues in Environmental; Science and Technology 23, 1-27, 2006.

This Note was prepared by a Working Party of the RSC Environment, Health and Safety Committee [EHSC]. The members of the Working Party were:

Paul Whitehead, Paul Illing, David Taylor, Steven Lipworth

This Note is also available on the RSC website: http://www.rsc.org