Hazard and Risk Assessment of Substances: The HSAC approach

EXECUTIVE SUMMARY

This paper summarises the views of the Hazardous Substances Advisory Committee (HSAC) concerning hazard and risk assessment of substances in the environment. Wherever possible, examples of adverse effects on ecological systems are used, since the remit of HSAC lies in this area. The legal framework governing chemical regulation is described and factors which may lead to inappropriate assessments are noted, along with the uncertainty attached to the process.

Evaluation of the harmful effects of substances in the environment may be based either upon hazard alone or upon an evaluation of risk. It always starts by identifying potential targets and routes of exposure. This is followed by hazard identification/characterisation with the option of proceeding to exposure assessment and risk identification/characterisation. A substance's potentially hazardous properties can include toxicity, persistence and ability to bio-accumulate. Risk is assessed by evaluating these properties against the predicted concentrations to which organisms are exposed. The hazard associated with a particular substance is its intrinsic ability to cause harm, while risk is the probability that such harm will occur in practice; it depends upon exposure, and the probability of risk from a particular hazard is almost always <100%.

The Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulations were implemented in 2007. They have the primary aim of ensuring a high level of protection of human health and the environment and place the onus for risk management on industry rather than on regulators. Under REACH, however, registrants only have to assess risks for the amount of substance they manufacture or import; risk assessments conducted under REACH may therefore underestimate environmental exposure to widely used chemicals.

The properties of some substances may make it difficult (or impossible) to define a safe level of exposure. Furthermore, it can be difficult to quantify the exposure of organisms in different environmental compartments. Where exposure is unclear but there is evidence that the substance has hazardous properties, the so-called Precautionary Principle may be invoked; however, this type of regulation tends to overestimate potential risks. Wherever possible, therefore, case by case risk assessments relying on good quality, comprehensive scientific evidence should be undertaken in order to ensure proportionate and effective regulation.

Uncertainty may compromise the reliability of risk assessments. The Precautionary Principle is driven by uncertainty, and there is debate as to the circumstances under which it should be invoked. The HSAC believes that uncertainty should be reduced as far as possible prior to decision-making, although this should not delay approval or regulatory action unnecessarily.

The HSAC recommends that potentially hazardous substances should be subjected to risk-based assessment, ideally on the basis of measured data rather than predictions or mathematical models. Access to full data packages capable of expert review is crucial for proper evaluation. We recognise, however, that this is not always feasible; in particular, difficulties may arise when commercial sensitivity hinders access to key data and we welcome initiatives aimed at encouraging data sharing.

In conclusion, the validity and usefulness of any risk assessment are based on many factors. A major consideration is the quality and comprehensiveness of the underpinning scientific evidence. Good regulatory decisions are most likely to result from the objective assessment of high quality evidence, taking into account all aspects of the risk assessment process.

CONTENTS

INTRODUCTION

It is important to strike the right balance between reaping socio-economic benefits from the use of substances and minimising the potential risks they pose. Potentially hazardous properties of a substance include its toxicity, persistence and ability to bio-accumulate[1]. Risk is the probability that a substance's hazardous properties will cause harm in practice and depends on exposure. It is assessed by relating these properties to the predicted concentrations to which humans or wildlife are likely to be exposed. The probability of risk from a hazard is almost always less than 100% and the level at which that risk is acceptable is determined by the context of the risk. Risk can be contextualized by means of procedures such as PESTLE assessment[2].

Independent expert scientific committees such as the Hazardous Substances Advisory Committee (HSAC; formerly the Advisory Committee on Hazardous Substances, ACHS) may be asked to consider evidence or provide guidance on issues relevant to the risk assessment of chemicals. This paper sets out the approach the HSAC recommends when considering evidence for the hazard or risk assessment of substances. Its aim is to encourage transparency and consistency in the approaches and methods used to assess hazard and risk.

Wherever possible, examples of effects on ecological systems are used because HSAC has a specific remit in this area. Ecological systems encompass specific natural resources or entire habitats, including plants and animals, as well as the physicochemical environment with which substances interact. Most of the examples presented involve individual substances that have been widely available for some time, since these tend to offer clear-cut, illustrative results; however, it is important to recognise that, in reality, humans and ecosystems are likely to be exposed to mixtures of chemicals by a variety of routes.

THE REGULATORY FRAMEWORK

Historically, chemicals regulation evolved to meet the need to control health hazards, for example by banning the use of individual substances or by restrictions on use, while environmental regulation evolved to protect or improve the environment. The two strands of regulation developed separately and independently of each other. By the last decade of the twentieth century there was growing recognition that the EU legislation then in force did not and could not provide sufficient protection for human health and the environment. As part of the means to address the problem, the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulations[3] entered into force in 2007. These refocused chemicals regulation, placing the weight of obligation on industry rather than on regulators with the primary aim of ensuring a high level of protection of human health and the environment.

Around the same time, work commenced to replace the Dangerous Substances Directive and the Dangerous Preparations Directive with the Classification, Labelling and Packaging of Substances and Mixtures, etc. (CLP) Regulation 2008[4]. These focus exclusively on the identification of hazardous properties of chemicals and for deciding on their classification, for both of which responsibility mainly lies with manufacturers, importers and downstream users of those

[1] For a glossary of terms used in ecotoxicology, see http://www.epa.gov/risk_assessment/glossary.htm
[2] HM Treasury (2004) The Orange Book; Management of Risk: Principles and concepts; http://www.hm-treasury.gov.uk/d/orange_book.pdf
[3] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2006R1907:20121009:EN:PDF
[4] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:en:PDF

substances or mixtures, regardless of whether they are subject to the requirements of REACH[5]. Further there is a duty to report to the European Chemicals Agency (ECHA) and a duty upon the ECHA to publish[6]. However, in some cases, the decision on the classification of a chemical is taken at Community level. This often concerns the most hazardous substances (substances of *very high concern*). These are usually carcinogenic, mutagenic, toxic for reproduction or respiratory sensitisers. If such a decision is taken it is mandatory for the suppliers of the respective substance or mixture to apply this harmonised classification and labelling.

Understanding the legal framework is essential to appreciating the risk assessment process. The basis on which the EU regulates the use of chemicals in various contexts is described further in Appendix 1. Chemical regulation in Europe does not conflate hazard and risk and there is provision within the regulations for risk assessment of some, but not all, substances.

RISK ASSESSMENT

The reader is referred to other sources (e.g. the Defra Guidelines for Environmental Risk Assessment and Management[7], the OECD environmental risk assessment toolkit[8] and the US EPA Risk Assessment Portal[9]) for comprehensive advice on risk assessment. The process involves three stages (i) hazard identification and characterization, (ii) exposure assessment and (iii) risk identification and characterization, each of which is described briefly below:

HAZARD IDENTIFICATION AND CHARACTERISATION

Screening tests must be amenable to testing many substances for:

- Physicochemical properties (e.g. flammability, boiling point, water solubility and relative density). These determine how a substance behaves in different environmental compartments and influence its degradability and persistence;
- Toxicological properties for humans such as irritancy, sensitisation, acute and chronic effects including carcinogenicity, mutagenicity and reproductive effects; and
- Ecotoxicological properties including acute and chronic toxic effects on different species as well as processes such as bio-accumulation and bio-magnification[10],[11].

For ethical, time and cost-saving reasons hazards may initially be predicted from molecular structure (*in silico*) available information on structurally similar chemicals (read-across) and short-term tests. These are conducted *in vitro* wherever possible in order to avoid the unnecessary use of animals, and recent improvements in miniaturization and robotics have allowed the development of a range of high throughput screening approaches[12]. Since the objective is to identify potential hazards, these initial screening tests tend to be biased towards increasing sensitivity at the expense of specificity.

The aim of further *in vivo* toxicity or bioaccumulation tests is to determine the nature and severity of an identified hazard towards target organism(s). Normally the most sensitive test

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[5] CLP Regulations recital (16)
[6] http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database
[7] http://www.defra.gov.uk/publications/2011/11/07/green-leaves-iii-pb13670/
[8] http://www.oecd.org/chemicalsafety/risk-assessment
[9] www.epa.gov/riskassessment/
[10] Gobas, F.A.P.C., and Morrison, H.A. (2000) Bioconcentration and Biomagnification in the Aquatic Environment; http://research.rem.sfu.ca/downloads/rem-610/readings/gobas.pdf
[11] http://www.epa.gov/pbt/
[12] Thomas, C.R. *et al* (2011) Nanomaterials in the Environment: From Materials to High-Throughput Screening to Organisms. *ACS Nano* **5**,13-20.

species is chosen; however these results can be misleading since the organisms chosen may not be representative of those which are actually exposed in the environment. In general, organisms are well adapted to coping with endogenous and exogenous chemicals and have evolved protective and detoxifying mechanisms so that for many endpoints, including those relevant for wildlife, a threshold concentration (one that is deemed to have no biologically relevant effect on, or significant accumulation in, humans or wildlife) may be assumed to exist.

Some substances are considered to meet the criteria for being of *very high concern* because it is not possible to define a threshold dose below which they have no adverse effects. Such substances are candidates for regulation by hazard alone; in particular, for uses where humans will be exposed without any clear personal benefit, or where suitable alternatives are available. Even for these substances, a threshold may be plausible under some circumstances, depending upon the results of characterization of modes of action and concentration-effect relationships[13].

The existence of thresholds for some substances has been questioned recently (e.g. for certain endocrine disrupters, although this is controversial) but it seems to hold true in the majority of cases. HSAC is not aware of any convincing reason to abandon the concept of toxicity thresholds.

EXPOSURE ASSESSMENT

It is exposure which determines whether a biological target, which may range from a single species to an entire ecosystem, is likely to experience adverse effects. Only if the target species is exposed to a harmful dose does a substance actually represent a risk. In order to model environmental exposures for each compartment, information on the following is required:

- Characteristics of the substance, e.g. source, distribution, concentrations, and physicochemical properties, degradation and accumulation; and
- Probability of exposure of the population or environment *via* all;
  - of a substance's uses and production and disposal
  - potentially relevant environmental compartments (e.g. fresh water, river sediment, identified during the conceptual model stage)

Inadequate techniques for measuring exposure and the uncertainty in predicting exposure can make it difficult or impossible to predict potential risks, despite the apparent availability of large amounts of toxicity data (see text box below, illustrating uncertainty in predictions of exposure exacerbated by lack of suitable analytical techniques to validate the predictions).

Extract from ACHS Report on Nanosilver[14]:

Exposure levels in the environment are not known. Modelled concentrations are approximately 100 ng L^{-1} potentially rising to ≥1 µg L^{-1}, dependent on uses, increase in usage and the behaviour of nanosilver within the environment. These aspects are incompletely understood.

It is often difficult to define the exposure of organisms in different environmental compartments accurately, but such exposure assessment is essential to successful risk assessment and reliable environmental exposure data should be sought wherever possible. Where attention has been paid to ensuring accurate estimation of potential exposure, using deterministic modelling followed by methods which represent real-life exposure and targeted monitoring of (in this

[13] COM (2010) Guidance statement : Thresholds for *in vivo* mutagens; http://www.iacom.org.uk/guidstate/documents/Thresholdsforinternetfinal.pdf
[14] ACHS (2009) Report on Nanosilver; http://archive.defra.gov.uk/environment/quality/chemicals/achs/documents/achs-report-nanosilver.pdf

example) human pharmaceuticals in the most vulnerable sources and final waters, estimates of exposure have become more realistic and tended to be lower[15].

The requirement for accurate exposure measurement has been highlighted by the debate concerning the potential adverse effects of neonicotinoid insecticides to which bees are exposed while foraging. Laboratory experiments indicate that, at 1-5 µg/l of the most toxic neonicotinoids in nectar, adverse effects are unlikely to be observed[16]; it is now important to determine whether exposure in the field is actually above, near to or well below that threshold.

RISK IDENTIFICATION AND CHARACTERIZATION

The objective of risk identification and characterisation is to assess the probability and extent of occurrence of adverse effects of chemicals in the environment realistically, taking into account predicted exposure conditions over time. The potential for induction of adverse effects at the most sensitive stages of development (e.g. the embryo or foetus) is particularly important.

(Eco)toxicological tests range from the assessment of adverse effects on individual species to comprehensive ecosystem studies. As a first step, the dose/concentration response of the observed effect (usually initially identified in a screening assay at high concentrations) should be characterised at environmentally relevant concentrations in order to determine whether it is likely to occur under the conditions which prevail in the environment. This makes it possible to express environmental risks in terms of the ratio between the worst-case Predicted Environmental Concentrations (PEC; derived from environmental exposure assessment) and Predicted No Effect Concentrations (PNECs) which are expected to be harmless to target ecosystems[17]. If the risk is low, a substance will generally be permitted for use, perhaps with some practical controls to limit exposure. Emerging approaches include the use of probabilistic risk assessments taking account of variability in hazard and exposure estimates.

Risk can be modulated by reducing exposure; this is part of the role of the risk manager. Under REACH, however, registrants only have to assess risks for their individual level of manufacture or import. Risk assessments conducted to meet REACH requirements are therefore likely to underestimate environmental exposure to widely used chemicals. Under the repealed Existing Substances Risk Assessment procedures there used to be a process for combining several individual exposure assessments into one; unfortunately, ECHA does not currently have a mechanism for conducting such a comprehensive assessment. The HSAC would like to see a similar process implemented under REACH.

UNCERTAINTY

All risk assessments are subject both to variability and uncertainty. Variability may be defined as observable diversity in biological sensitivity or response, and in exposure parameters[18]; the effects of data variability on risk assessment can be measured but cannot be reduced.

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[15] DWI 70/2/231, ACHS Workshop on Pharmaceuticals in the Environment, workshop-presentations 110131, P. Marsden; http://archive.defra.gov.uk/environment/quality/chemicals/achs/

[16] Defra (2013) An assessment of key evidence about neonicotinoids and bees; www.gov.uk/government/publications/an-assessment-of-key-evidence-about-neonicotinoids-and-bees

[17] http://www.oecd.org//chemicalsafety/assessmentofchemicals/theoecdenvironmentalriskassessmenttoolkitstepsinenvironmentalriskassessmentandavailableoecdproducts.htm

[18] COT (2007) Report on Variability and Uncertainty in Toxicology of Chemicals in Food, Consumer Products and the Environment; http://cot.food.gov.uk/pdfs/vutreportmarch2007.pdf

Uncertainty may be defined as imperfect knowledge concerning the present or future state of an organism, system or (sub) population under consideration[15] and is inherent to the process of predicting the probability, frequency and severity of known or potential adverse effects. Determinable uncertainty may be reduced by the acquisition of better evidence. The level of uncertainty depends on many factors, including the quality of the evidence, the variability of the data, the assumptions, working hypotheses and conjectures made at each stage of the process. Additional uncertainty may be generated when prediction or testing is removed from the effect of a substance on a target organism, e.g. by using *in vitro* tests or *in silico* predictions.

Uncertainty owing to lack of knowledge cannot be quantified, but may be reduced by adequate scoping of the problem. All assessments should start with a conceptual model which ascertains:

- the source, pathway (or routes) of exposure;
- the target organisms under consideration; and
- whether there are any particularly vulnerable or sensitive target organisms that need to be considered.

This process helps to clarify the context of the risk assessment and any legal requirements, as well as providing it with focus and boundaries.

Failure to take all factors into account in a risk assessment may have catastrophic consequences. One example is the dramatic decline in populations of three species of Asian vultures caused by accumulation of uric acid (visceral gout), attributed to the atypical veterinary use of diclofenac in cattle and their particular means of disposal in parts of Asia – so-called 'air burial'. This effect was not predicted on the basis of any of the routine toxicity tests or risk assessment procedures as the mode of action does not occur in standard test species[19], and highlights the fact that no regulatory scheme for substances can be guaranteed to be comprehensive in identifying significant risks. It is interesting to speculate whether, with a risk based approach and consideration of pathways to exposure, someone might have connected the use of diclofenac in cattle in parts of Asia to vultures being exposed to the substance.

SAFETY FACTORS

The conventional approach to dealing with uncertainties in risk assessment is to apply so-called safety or assessment factors[20,21].; that is, acceptable exposure is based on the lowest dose which has a measurable effect (e.g. the NOAEL [No Observable Adverse Effect Level] or, in some cases, a benchmark dose taken from the dose response curve) divided by factors which allow for interspecies differences and inter-individual variability. The factors usually applied when conducting a human risk assessment are 10 fold for interspecies differences (i.e. to allow for possible differences in response between experimental animals and humans) and 10 fold for inter-individual variability (i.e. to allow for differences between individuals within a human population), giving an overall safety factor of 100 fold. In addition, it has been suggested that the standard 10 fold safety factors could be subdivided into smaller adjustment factors which specifically allow for chemical-specific toxicokinetic and toxicodynamic variability[22].

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[19] Oaks, J.L. *et al* (2004). Diclofenac residues as the cause of vulture population decline in Pakistan *Nature* **427**: 630–3

[20] OECD (1992) OCDE/GD(92)169 Environment Monograph No. 59 Report of the OECD Workshop on the extrapolation of laboratory aquatic toxicity data to the real environment; http://www.oecd.org/chemicalsafety/testing/34528236.pdf

[21] IGHRC (2003) Uncertainty Factors: Their use in human health risk assessment by UK Government; http://ieh.cranfield.ac.uk/ighrc/cr9.pdf

[22] Dorne, J.L. and Renwick, A.G. (2005) The refinement of uncertainty/safety factors in risk assessment by the incorporation of data on toxicokinetic variability in humans. *Toxicol Sci.* **86**:20-26

The size of environmental assessment factors varies depending on the data available and is generally x100-1000 for acute data and x10-x100 for chronic data. There are many other sources of uncertainty in environmental risk assessment; these include:

- possible interactions with other chemicals;
- effects of weather and other stressors;
- how to relate effects seen in the lab to possible effects on populations in the field; and
- predicting the effects of nanomaterials.

Additional safety factors may be applied in order to allow for these factors.

THE PRECAUTIONARY PRINCIPLE

In some cases it is impossible to identify a "safe" level of exposure to a substance, either because a NOAEL cannot be identified or because the shape of the dose response curve indicates that there is no threshold below which the absence of adverse effects can be guaranteed. The main categories to which this applies are substances which are:

- Carcinogenic, mutagenic and toxic for reproduction (CMR). For these compounds it is assumed that there is no concentration that is without risk;.
- Very persistent and very bio-accumulative (vPvB). These can travel long distances around the globe and build up to harmful levels in humans and wildlife, thus making the relevant exposure concentrations very difficult to predict; or
- Persistent, bio-accumulative and toxic (PBT).

The Precautionary Principle, which is enshrined in the Treaty on the Functioning of the European Union, provides a mechanism by which to reduce harm from these substances, or where uncertainty or data gaps preclude a confident risk assessment. Article 191.2 provides that Union policy on the environment shall be based on the Precautionary Principle and on the principle that preventive action should be taken. Article 191.3 states that "In preparing its policy on the environment, the Union shall take account of, *inter alia*, available scientific and technical data, the potential benefits and costs of action or lack of action and the economic and social development of the Union as a whole and the balanced development of its regions."

The Precautionary Principle is not actually defined by treaty. In 2000 the Commission Communication on the Precautionary Principle[23] was published with the stated aims of:

- outlining the Commission's approach to using the Precautionary Principle;
- establishing Commission guidelines for applying it;
- building a common understanding of how to assess, appraise, manage and communicate risks that science is not yet able to evaluate fully; and
- avoiding unwarranted recourse to the precautionary principle, as a disguised form of protectionism

Two years later a paper identifying three categories of uncertainty in relation to risk assessment was published by a member of the Group of Policy Advisers, European Commission[24]. It defines the three categories of uncertainty as uncertainty in effect, uncertainty in cause and uncertainty

[23] Commission of the European Communities (2000) Communication from the Commission on the Precautionary Principle; http://ec.europa.eu/dgs/health_consumer/library/pub/pub07_en.pdf

[24] Rodgers, M.D. (2003) Risk analysis under uncertainty, the Precautionary Principle and the new EU chemicals strategy *Regul. Toxicol. Pharmacol.* **37**, 370-81

in the relationship between a hypothesised cause and effect. The paper then sets out three broad descriptions of the Precautionary Principle:

- uncertainty justifies action;
- uncertainty requires action; and
- uncertainty requires a reversal of the burden of proof for risk assessments to the proponents of the activity; it is this point that has been enshrined in REACH.

The Precautionary Principle is explicitly incorporated in REACH, but because it is driven by uncertainty there is debate as to the quantity and quality of evidence required to invoke it. Two attempts to clarify the interpretation in the European Court are presented in Appendix 2.

PROPORTIONATE RESPONSE

A prudent approach to environmental protection, health or safety could be to opt for the worst-case hypothesis. This may result in control measures with unintended and undesirable consequences, including restrictions on the use of beneficial materials whose risks could have been managed satisfactorily. A more considered approach might be to adopt an approach based upon pragmatic precaution, as advocated by the Royal Society of Chemistry[25].

As originally defined (in the German 'Vorsorge Prinzip'), the scale of the response to a perceived threat must be in proportion to the scale of the threat. For example, synthetic estrogens are found in treated sewage and in many rivers, but UK fish populations are not in massive decline even though feminisation of males in certain species is causing reproductive damage and may have impoverished some fish communities. Many would consider it disproportionate to ban the use of ethinyl estradiol in the contraceptive pill, or even to insist on its removal from drainage water, on the basis of this evidence[26]. Activated carbon filtration is able to remove a large proportion of the oestrogens from treated sewage[27,28], but its cost would be prohibitive if applied to all sewage treatment plants and is probably unnecessary given that many effluents and/or receiving waters are only mildly contaminated with oestrogens[29]. A more nuanced approach, such as the gradual introduction of improved sewage treatment only at those sites where sewage effluent is known to be damaging an entire ecosystem, may be required.

The law of unintended consequences should always be considered. An example is the use of methyl tert-butyl ether (MTBE) as an anti-knocking agent in petrol[30]. The use of lead as an anti-knocking agent is believed to have led to widespread neurotoxicity, and such use is now being phased out because this effect appears to have no threshold. MTBE was substituted for lead during the 1970s and 1980s. The use of MTBE helped to reduce harmful air emissions of lead, but also has caused widespread contamination by MTBE of US drinking water supplies. The

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[25] RSC (2009) Environment, Health & Safety Committee: Discussion note on pragmatic precaution; http://www.rsc.org/images/PragmaticPrecaution_tcm18-159553.pdf

[26] Sumpter, J.P. and Jobling, S. (2013). The occurrence, causes, and consequences of estrogens in the aquatic environment. *Environ. Toxicol. Chem.* **32**, 249-251.

[27] Grover, D.P. *et al* (2011). Endocrine disrupting activities in sewage effluent and river water determined by chemical analysis and in vitro assay in the context of granular activated carbon upgrade. *Chemosphere* 84, 1512-1520.

[28] Baynes, A. *et al* (2012). Additional treatment of wastewater reduces endocrine disruption in wild fish – a comparative study of tertiary and advanced treatments. *Environ. Sci. Technol.* **46**, 5565-5573.

[29] Jobling, S. *et al* (2006). Predicted exposures to steroid estrogens in UK rivers correlate with widespread sexual disruption in wild fish populations. *Environ. Health Perspect.* **114** Suppl.1, 32-39.

[30] Von Krauss, M.K. and Harremoës, P. (2001) MTBE in petrol as a substitute for lead; in EEA (2001) Late Lessons from Early Warnings: The Precautionary Principle 1896-2000 (Report No 22/2001); http://www.eea.europa.eu/publications/environmental_issue_report_2001_22/issue-22-part-11.pdf/view

aesthetic impact of MTBE contamination of groundwater is considerable since its potent terpene-like odour is detectable at very low concentrations. Relatively small amounts of MTBE may thus render large reserves of groundwater useless. When the taste and odour threshold in water is exceeded, contaminated drinking water is normally not used, requiring the utilisation of alternative supplies. The costs of remediation are high. Concerns in particular over the potential for contamination of groundwater supplies have prompted regulatory authorities in western nations to reassess the risks associated with the use of MTBE [31].

THE HSAC APPROACH TO DATA EVALUATION

It has been suggested that one of the reasons for a delay in regulatory action is the scientific process itself[32] and that lower strengths of evidence than those normally used to adduce causality should be employed to avoid 'paralysis by analysis', permitting action when there are reasonable grounds for concern[33]. The HSAC holds that standards of evidence should not be lowered with the sole aim of speeding up the process, since this can lead to poor regulatory decisions. It appreciates that the quest for incontrovertible evidence should not delay effective regulation, but questions hasty decision-making based on hazard alone. However, it recognises that even strong regulatory action cannot necessarily completely remediate the damage caused by highly persistent and toxic materials once they have escaped into the environment: this emphasises the need for rigorous environmental risk assessment of new chemicals[34].

EVALUATION OF TEST PREDICTABILITY

The Bradford Hill Criteria[35] (namely temporality, strength of the association, consistency of the observations, biological plausibility of the effect and evidence for recovery following diminution of the stressor) are pointers to establishing causality. These pointers were originally used to evaluate epidemiological data. Toxicology has expanded since then; *in vivo*, *in vitro* and *in silico* tests are now used as substitutes for observations in humans. If an early screening test or prediction is substituted for evidence which indicates a causal association between substance and adverse effect, two key questions arise:

- How often will it predict an adverse effect which will not translate into a risk in practice?
- How often will it fail to predict a potential risk?

For example, the pesticide methoxychlor does not act as an oestrogen mimic in *in vitro* receptor binding assays in the absence of metabolic activation, but does cause feminisation in fish *in vivo* as a result of activation to an oestrogenic metabolite[36].

HSAC supports the continuing development of better ways to predict risk, particularly by seeking non-animal based methods of testing. As expressed in its Statement on the Use of Animals in Chemical Testing[37], "HSAC fully supports the aims and requirements of the REACH

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[31] http://www.clu-in.org/contaminantfocus/default.focus/sec/Methyl_Tertiary_Butyl_Ether_%28MTBE%29/cat/Overview/

[32] EEA (2001) Late Lessons from Early Warnings: The Precautionary Principle 1896-2000 (Report No 22/2001); http://www.eea.europa.eu/publications/environmental_issue_report_2001_22

[33] EFSA (2013) Scientific Opinion on the hazard assessment of endocrine disruptors: Scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. *EFSA Journal* **11**:3132

[34] Matthiesen, P. (2013) Detection, monitoring and control of tributyltin – an almost complete success story. *Environ. Toxicol. Chem.* **32**: 487-489

[35] Bradford-Hill A. (1965) The environment and disease: Association or causation? *Proc. R. Soc. Med.* **58**, 295-300.

[36] Ankley, G.T. *et al* (2001). Description and evaluation of a short-term reproduction test with the fathead minnow (*Pimephales promelas*). *Environ. Toxicol.* Chem. **20**, 1276-1290.

[37] HSAC (2012) Statement on the Use of Animals in Chemical Testing; http://www.defra.gov.uk/hsac/files/statement-use-of-animals-in-chemical-testing.pdf

Regulation to reduce, refine and replace animal testing wherever possible, through the avoidance of test duplication and repetition, the mandatory sharing of animal test data, the use of non-animal alternative test methods where available, and the use of animal testing only as a last resort. The HSAC would prefer a minimisation of, and ultimately an end to, animal testing for chemical safety assessment, provided that the current level of protection for human beings and the environment from chemicals is maintained. Advances that lead to the development of appropriate alternatives to using intact animals which are sufficiently sensitive and specific to enhance accurate prediction of risk to intact organisms are keenly anticipated."

ACCESS TO DATA

Full access to key data is crucial; a summary or opinion is usually insufficient to allow a judgment to be formed. Studies performed and reported according to the Good Laboratory Practice (GLP) guidelines have the benefit of a minimum assured standard and should provide sufficient information to allow the study to be repeated.

Commercial sensitivity may hinder access to data. The European Food Safety Authority (EFSA) recently announced the launch of a major initiative designed to facilitate access to data, enhancing transparency in risk assessment[38]. This programme will consider how best and to what extent technical data used in risk assessments can be made available to the broader scientific community and interested parties. Under REACH, ECHA makes available robust study summaries of all the physicochemical, toxicological and ecotoxicology data in the submitted dossier unless a claim of confidentiality is made[39]. The HSAC welcomes all such initiatives.

STANDARD OF REPORTING IN THE PUBLISHED LITERATURE

HSAC encourages a minimum standard of reporting in the published literature (see text box, below). The presentation of sufficient information to interpret a study is encouraged by, for example, providing historical negative control data. Conversely the presentation of derived data only, where it is impossible to see the original negative control data, is discouraged.

Extracts from HSAC opinion on nanomaterials[40]

"Prior to assessment of biological uptake and effects, there is a need for higher, more consistent standards in nanoparticle (NP) characterisation, in dose measurement and in their reporting to a wider audience. Minimum requirements include the rationale for the choice and provenance of the nanoparticles, appropriate sample pre-treatment, physical and chemical characterization, appropriate formulation and measurement of actual, as opposed to nominal, dose. The dynamic nature of nanoparticles during exposure also needs to be taken into account. The details of the above considerations and the metrological analysis should be fully reported; without such information the assessment of biological effects is of doubtful value."

ASSESSMENT OF INDIVIDUAL STUDIES

Consistency in the assessment of (eco)toxicity data promotes robust decision-making[41,42,43]. All attempts to improve the quality of data interpretation are welcomed by HSAC. Key factors are[44]:

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[38] http://www.efsa.europa.eu/en/press/news/130114.htm

[39] http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

[40] HSAC (2012) Nanomaterials: Physico-chemical properties and dose considerations required before assessment of biological behaviour; http://www.defra.gov.uk/hsac/files/HSAC-Opinion-on-Nanoscience.pdf

[41] Klimisch H. J., Andreae, M. and Tillmann, U. (1997) A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regul. Toxicol. Pharmacol. 25*, 1–5

- **Reliability:** the fitness for purpose and the standard to which it is conducted (e.g. OECD guidelines followed, information supplied, appropriateness of controls, test conditions, sample sizes etc);
- **Plausibility**: the appropriateness of the study and the strength of measured effect at relevant concentrations will contribute to its biological and environmental relevance. High quality studies may provide information to allow assessment of reasons for inconsistent results etc. Measured data are likely to be more reliable than predictions (e.g. read-across, QSARs etc); and
- **Relevance**: positive and negative effects should be examined in relation to other knowledge to assess the significance that should be attached to the results.

Reliable, relevant and plausible studies score highly and carry greater weight according to these criteria, while weaker data could only be considered as supportive evidence. This approach, which is being evaluated in an international collaborative programme co-ordinated by the Oekotoxzentrum Centre Ecotox in Switzerland[45], should allow the identification of gaps that could be filled promptly and make the process of considering different lines of evidence and the amount of support that each line gives to a decision more transparent.

QUANTITY AND QUALITY OF DATA SETS

It is self-evident that a conclusion supported by a large amount of relevant data is likely to be more reliable than one supported by fewer, less relevant data. Data sets range from very sparse information to very large and complex data sets, comprising data from regulatory studies and the published literature. In the former case, evidence may be sought from other sources using information from chemical entities with similar structures; this is known as read-across and is a key part of the REACH approach. In the latter case, it should noted that large data sets *per se* do not necessarily equate to an adequate weight of evidence; key information may still be missing (see text box, below, showing how the absence of key studies may affect the advice given, and lead to calls for further work, even where there is a large body of evidence).

Extracts from ACHS opinion on decabrominated diphenyl ether (decaBDE)[46]

"Poor aqueous solubility makes it difficult to analyse in environmental matrices and its many potential breakdown products, arising from historic and current use of other parent materials as well as from deca-BDE, make it difficult to identify degradation products in the environment. The analytical challenges associated with quantifying congeners differing in degree of debromination mean that most studies have not identified degradation products, or have only analysed a few potential products, and contamination due to previous commercial use of degradation products is also a confounding factor.

Paradoxically, the evidence for environmental degradation provides reassurance that deca-BDE is not extremely persistent, but simultaneously raises concerns about its potential to be transformed to SVHCs. It would appear that deca-BDE lies on the borderline of the "very persistent (vP)" classification. For example, there is evidence for significant breakdown of deca-BDE, yet the resulting half-life in soil is >180 days, meeting

[42] ILGRA (1999) Risk assessment approaches used by UK Government for evaluating human health effects of chemicals; http://ieh.cranfield.ac.uk/ighrc/cr2.pdf

[43] Bowden, R.A. (2004) Building confidence in geological models. *Geological Society, London, Special Publications* **239**, 157-173.

[44] Kase, R. *et al* (2012) Klimisch 2.0 – Raising the bar to increase the scientific quality of environmental risk assessments; http://www.oekotoxzentrum.ch/projekte/klimisch/doc/setac2012

[45] http://www.oekotoxzentrum.ch/projekte/klimisch/index_EN

[46] ACHS (2010) ACHS opinion on decabrominated diphenyl ether (decaBDE); http://archive.defra.gov.uk/environment/quality/chemicals/achs/documents/achs-decaBDE-opinion-100923.pdf

the criterion for a vP compound.
The ACHS recognises that this conclusion is, of necessity, based upon the results of a single study. The Huang soil/plant study is a reliable study but was carried out under artificial light and at 20/25°C. It is therefore difficult to extrapolate to rates of formation of the degradation products meeting the SVHC criteria in typical outdoor locations.
Circumstantial evidence indicates that there is potential for deca-BDE to debrominate in the environment to substances that are of concern (e.g. hexa- and heptaBDE). The ACHS recognises that independent verification of the soil/plant study, plus a possible dust study considering photodegradation, may be prudent and desirable".

CONCLUDING REMARKS

One of the HSAC's terms of reference is to advise officials, UK Ministers, including Ministers in the Devolved Administrations, and other relevant bodies "*on research needs and other evidence gaps relating to potentially hazardous substances and articles, including nanomaterials; including analysing, interpreting, and assessing the quality and relevance of evidence*."

The HSAC recommends risk-based approaches to the assessment of potentially hazardous substances and for safety assessment of substances on a case by case basis, unless convincing evidence is provided to the contrary. There is provision for risk assessment in European regulation of chemicals, although the Precautionary Principle probably means that the assessment will err on the side of caution. Conclusions should ideally be based upon measured data rather than on predictions or mathematical models, and access to full data packages capable of expert review is crucial for proper evaluation. We recognise, however, that this is not always feasible; in particular, difficulties may arise when commercial sensitivity hinders access to key data and we welcome initiatives aimed at encouraging data sharing.

Uncertainty should be reduced wherever possible, although approval/regulatory action should not be delayed where there are sufficient grounds to proceed. A number of issues remain contentious, particularly in relation to endocrine disrupters; these include:

- the inability to identify "safe" thresholds for exposure to some substances;
- the question of whether the timing rather than the amount of exposure is critical in causing harm; and
- the assertion that inconsistency between research results is not a strong reason for dismissing possible causal links.

The conclusions of the latest European Environment Agency (EEA) Report[47] could be interpreted as recommending a hazard-based approach to safety assessment. On the other hand EFSA recently concluded that, at least for endocrine disrupters, risk assessment taking into account both hazard and exposure makes optimal use of the available information[48].

The validity and usefulness of any risk assessment are based on many factors. A major consideration is the quality and comprehensiveness of the underpinning scientific evidence. Good regulatory decisions are most likely to result from high quality evidence, taking into account all aspects of the risk assessment process.

[47]EEA (2013) Implications for science and governance (Report No 1/2013);
http://www.eea.europa.eu/publications/late-lessons-2/part-e-implications-for-science

[48]EFSA (2013) Scientific Opinion on the hazard assessment of endocrine disruptors: Scientific criteria for identification of endocrine disruptors and appropriateness of existing test methods for assessing effects mediated by these substances on human health and the environment. *EFSA Journal* **11**:3132

APPENDIX 1: CHEMICALS REGULATION IN EUROPE

REACH

Some of the key provisions of REACH are based on risk assessments, for example the chemical safety report that in many cases has to be included in the registration dossier (see Annex 1) and Chapter 2 of Title VI which deals with prioritisation of substances for evaluation using a risk based approach. However, other provisions rely on hazard classification only: for example, where it is not possible to specify a no-effect level for substances then an authorisation cannot be granted on the basis of risk (REACH specifies that this applies to PBT, vPvB substances plus some other substances, where a no-effect level cannot be defined). In such cases 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.

It should also be noted that under Article 55 of the Authorisation part of REACH it is stated that the "aim of this Title is to ensure the good functioning of the internal market whilst 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".

Norlander et al[49] point out that hazard classification of chemicals under the CLP Regulation can trigger automatic consequences under REACH without any requirement for a risk assessment.

The Medicinal Products Directive[50]

Acknowledges that medicinal products may be associated with risks for human health, but allows the marketing of such products if the positive therapeutic benefits outweigh these risks.

Directives relating to food or feeding stuffs

These cover use as food additives, flavourings in foodstuffs, as additives in feeding stuffs and also in animal nutrition. Two examples are:

- **Food Law Regulation 178 of 2002[51]**

  In which Article 6 provides that "in order to achieve the general objective of a high level of protection of human health and life, food law shall be based on risk analysis except where this is not appropriate to the circumstances or the nature of the measure". Risk is defined in Article 3 as a function of the probability of an adverse health effect and the severity of that effect, consequential to a hazard. Article 7 relates to the application of the Precautionary Principle in the following terms: where "the possibility of harmful effects on health is identified but scientific uncertainty persists, provisional risk management measures necessary to ensure the high level of health protection chosen in the Community may be adopted, pending further scientific information for a more comprehensive risk assessment." Article 6.2 provides that such measures must be proportionate and no more restrictive of

[49] EJRR 3|2010 Hazard v Risk in EU Chemicals Regulation p244
[50] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20110721:EN:PDF
[51] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:031:0001:0024:EN:PDF

trade than is necessary regard being had to technical and economic feasibility and other factors regarded as legitimate in the matter under consideration.

- **Additives for use in Animal Nutrition Regulation 2003**[52]

  Where preamble (17) acknowledges that "scientific risk assessment alone cannot, in some cases, provide all the information on which a risk management decision should be based, and that other factors relevant to the matter under consideration should legitimately be taken into account, including societal, economic or environmental factors, feasibility of controls and the benefit for the animal or for the consumer of animal products." Interestingly the preamble continues "therefore, the authorisation of an additive should be granted by the Commission". So in this example proportionate measures are used to allow the authorisation rather than, as in the previous example, to prevent use.

Cosmetics Regulation 2009[53]

This Regulation replaces the Cosmetics Directive as of 11 July 2013. It uses the term "safety assessment" rather than "risk assessment" and provides that an appropriate weight-of-evidence approach is used in the safety assessment for reviewing data from all existing sources. By monitoring the composition and labelling of products, it aims to ensure that consumers' health is protected and that they are well informed,. However, with certain exceptions, the Regulation also prohibits substances classified as CMR substances, thus utilizing the hazard approach only.

Plant Protection Products Regulation 2009[54]

This Regulation lays down rules for the assessment and authorization of plant protection products in commercial form and for their placing on the market, use and control within the EU. The Regulation increases the level of health and environmental protection. However, with certain exceptions, the regulation prohibits substances classified as CMR substances – again, utilizing the hazard approach only.

Biocidal Products Regulations[55]

Preamble (12) provides that "with a view to achieving a high level of protection of human health, animal health and the environment, active substances with the worst hazard profiles should not be approved for use in biocidal products except in specific situations." Accordingly, substances classified as CMR substances in category 1A and 1B are, with some exceptions, prohibited. The regulations also prohibit endocrine disruptors and, until a definition is agreed, it requires all CMR substances in category 2 to be considered as endocrine disruptors. The regulation also bans PBT and vPvB substances. However, preamble (32) provides that in other cases applicants should submit dossiers which contain the necessary information for evaluation of the risks that would arise from proposed uses of biocidal products. So once more a dual approach is adopted to reflect the probable different impacts of use.

Earlier versions of some of these Regulations incorporated a ban based on hazard. It is clear from what is said above however, that these blanket bans have been relaxed, although only on a case by case basis.

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[52] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:268:0029:0043:EN:PDF
[53] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:0209:EN:PDF
[54] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:309:0001:0050:EN:PDF
[55] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:167:0001:0123:EN:PDF

APPENDIX 2: THE PRECAUTIONARY PRINCIPLE

Several attempts have been made in the European court to clarify the position of the Precautionary Principle in chemicals regulation. Two of many notable judgments are provided.

Pfizer (T13/99) attempted to overturn a ban imposed by the Commission on the use of virgiamycin. Grounds included the misapplication of the Precautionary Principle. The Commission commissioned a report from SCAN as to whether the findings of an initial scientific report "were scientifically justified" and, *inter alia*, whether the risk was a hazard. In their report SCAN said that "the use of virginiamycin as a growth promoter does not constitute an immediate risk to public health in Denmark" but also that " it is of the opinion that a full risk assessment cannot be made until quantitative evidence of the extent of transfer of antimicrobial resistance from livestock sources is obtained and the significance of this within the overall use of antimicrobials for clinical and non-clinical purposes evaluated" According to SCAN, this was an uncertain risk but not an immediate hazard and viewed that monitoring by the Danish government and the EU would enable [detection of] any significant increases in the resistance, should that occur." The Commission disagreed because there was uncertainty and a ban was imposed. Litigation followed and Pfizer were unsuccessful.

In the later case of Solvay Pharmaceuticals BV ECJ Case T-392/02 the court said at paragraph 130 " To make the maintenance of the authorisation of a substance subject to proof of the lack of any risk, even a purely hypothetical one, would be both unrealistic — in so far as such proof is generally impossible to give in scientific terms since 'zero risk' does not exist in practice[i]… and contrary to the principle of proportionality" In a particularly impenetrable paragraph the judgment goes on to say "135. Recourse to the precautionary principle does not necessarily imply urgency. The adoption of a precautionary measure in order to prevent a risk which cannot be demonstrated in the state of scientific knowledge at the date of that adoption, but which is supported by sufficiently serious evidence, may in certain cases be deferred on the basis of the nature, the seriousness and the scope of that risk on the basis of a balancing of the various interests involved." So perhaps zero risk is not the objective of the Precautionary Principle.

[i] See, to that effect judgments in Pfizer Animal Health v Council at paragraph 145, and Alpharma v Council, at paragraph 158