

Discussion Articles

Effect Thresholds and 'Adequate Control' of Risks

The fatal flaws in the EU Council's position on Authorisation within REACH

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* Corresponding author (d.santillo@ex.ac.uk)DOI: <http://dx.doi.org/10.1065/espr2006.08.336>**Abstract**

Background. Preparation of the new European REACH (Registration, Evaluation and Authorisation of CHemicals) regulation on chemicals has reached a critical stage. Depending on how key elements of the legislative proposal are finalised, especially that on authorisation of uses of 'substances of very high concern', REACH could either provide an effective measure to drive innovation towards cleaner and safer alternatives, or instead lead to further avoidable chemical exposures on the basis of demonstrated 'adequate control' of risks. Given that some key indicators of human and wildlife reproductive health continue to decline in parts of Europe, while evidence for chemical exposure as a contributory factor grows, it will clearly be vital to get the legislation right.

Goal and Scope. Whereas there is now a consensus between the European Parliament and Council of the European Union that uses of persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) substances should only be permitted when no safer alternatives are available, major differences remain regarding the manner in which other 'substances of very high concern' (including substances which are carcinogenic, mutagenic or toxic to reproduction (CMRs) and endocrine disruptors) are addressed. This paper examines those differences in more detail and proposes some ways forward.

Methods. Using case studies of specific chemicals as examples, the paper critically evaluates the concepts of 'effect thresholds' and 'adequate control' of risks, which underpin the Council's proposal for many CMRs and endocrine disruptors.

Results. The subjectivity and uncertainties inherent in the threshold approach proposed by the Council, as illustrated by these case examples, bring its ability to ensure a high level of protection for the environment and human health into question:

- i. the nature and extent of toxic effects recorded depend on many different factors, including the type of test and conditions selected, the organisms exposed, the timing of exposure and precisely which effects are measured and over what timeframe.
- ii. doses considerably below 'no effect levels' for survival could nevertheless be causing significant impairment to health and/or reproductive success.
- iii. chemicals present in mixtures at levels below established thresholds for effects may, in combination, induce significant toxicological responses.

Discussion. Under the Council's current proposal, companies will be granted authorisations for some uses of CMRs and endocrine disruptors, even if safer alternatives without these properties are already on the market. The high level of evidence required for identification of substances as being of equivalent concern represents an additional weakness in the Council approach.

Conclusions. Instead, a requirement (along the lines of the Parliament's proposals) to address the availability of alternatives in all cases, to use them when available and to initiate their development when not, represents a more robust, defensible and protective approach to the management of 'substances of very high concern'. The possibility for authorisation of essential uses would remain, while all avoidable uses and exposures would progressively be prevented and sustainable innovation supported.

Perspectives. In the long run, this can only lead to a more sustainable future for the chemical industry in Europe, as well as delivering benefits of increased protection for our environment and health for generations to come.

Keywords: CMR; effect threshold; endocrine disruptors; Europe; hazardous chemicals; legislation; PBT; precautionary principle; REACH; risk assessment

Introduction

The European Commission's White Paper on a strategy for a future chemicals policy (EC 2001a), born out of widespread recognition of the failure of existing legislation and published in February 2001, promised a groundbreaking new approach to the evaluation and control of hazardous chemicals, including an intention "to phase out and substitute the most dangerous substances" (EC 2001b).

By the time of their publication in October 2003, the European Commission's formal REACH proposals (EC 2003) were already far less ambitious. Nevertheless, some of the foundations of a new system of chemicals management were emplaced, foundations which, if properly developed and implemented, could begin to provide the high level of protection for human health and the environment enshrined in the Treaty.

Aside from requirements for registration of chemicals and accompanying submission of basic data on properties and hazards (which have been drastically reduced), the key components of REACH designed to address and, as far as possible, prevent exposure to the 'most dangerous substances' are the Titles on Authorisation and Restrictions. Of these, Authorisation (the requirement that uses of so-called 'substances of very high concern' be permitted only if positively authorised) represents a substantially new approach to chemical regulation, intended to complement, rather than replace, the more traditional restrictions approach¹. If applied rigor-

¹ In the first instance, the Restrictions component of REACH represented by Annex XVI, will largely be transcribed from the equivalent annex of the existing marketing and use Directive 76/769

ously, such that only those continued uses which are clearly justified and unavoidable receive authorisations, then this element of the legislation could contribute greatly to reducing and ultimately eliminating exposure to some of the most hazardous chemicals in commerce, ensuring they are replaced instead with safer alternative substances or technologies.

A number of recent declarations by scientists and doctors illustrate the urgency for action on the most problematic chemicals, highlighting deeply worrying trends in reproductive disorders and cancers in wildlife and humans across many parts of Europe, as well as the gathering evidence that exposures to carcinogens, chemicals toxic to reproduction and those with endocrine disrupting properties are contributing to these trends. For example, the Paris Appeal issued in May 2004 by a diverse group of scientists, medical practitioners and jurists, among others, highlight upward trends in infertility, particularly male infertility, and in paediatric cancers in some industrialised countries (The Paris Appeal 2005).

Similarly, the Prague Declaration on Endocrine Disruptors, signed by more than 120 leading research scientists from across Europe in June 2005 noted serious concerns regarding prevalence of reproductive disorders and cancers among boys and young men in Europe, stressing that impacts in wildlife, while significant in their own right, may also provide early warnings of effects so far unobserved in humans (The Prague Declaration 2005).

1 European Parliament and Council of the European Union Positions on Authorisation

Following extensive discussions, both the European Parliament (EP 2005) and the Council of the European Union (Council of the European Union 2005) adopted their first formal positions on REACH in the latter part of 2005. There is now a clear agreement that the category 'substances of very high concern' (to be listed in Annex XIII in accordance with Article 54 of the REACH proposal) should include:

- substances which are classified as carcinogenic, mutagenic or toxic to reproduction category 1 or 2, in accordance with Directive 67/548 (so-called CMRs) (Article 54(a)–(c))
- substances which are persistent, bioaccumulative and toxic (PBTs) (Article 54(d)) and
- substances which are very persistent and very bioaccumulative (vPvBs) (Article 54(e)).

On the definition of the remaining group in this category, namely those substances which do not meet the criteria above but nevertheless give rise to equivalent concern on a case-by-case basis (Article 54(f)), significant disagreement remains. The Council requires 'scientific evidence of probable serious effects to humans or the environment which give rise to an equivalent level of concern' for such substances to be identified as presenting 'very high concern', while the Parliament proposes the more generic and precautionary text 'giving rise to a similar level of concern'². This difference has serious implications for the regulation, for example, of endocrine disrupting chemicals, which, in the continued absence of clearly defined criteria and the limits to the relevance for en-

docrine effects of data sets required as standard for registration purposes under REACH, will inevitably need to be addressed under the equivalent concern route for the foreseeable future. These issues also require urgent resolution, but are addressed in more detail elsewhere (WWF 2006).

Over and above this difference in proposed scope, however, lies a more fundamental disagreement between Parliament and Council regarding the purpose and mechanics of Authorisation, relating in particular to Article 57 of the REACH proposal and, more specifically, to the manner in which CMRs and substances of equivalent concern will be addressed.

The Parliament proposes that, for all 'substances of very high concern', including CMRs and substances of equivalent concern (Article 57):

"2. An authorisation shall be granted **only** if:

- (a) suitable alternative substances or technologies do not exist, and measures are in place to minimise exposure, **and**
- (b) it is demonstrated that the social and economic advantages outweigh the risks to human health or the environment which arise from the use of the substance, **and**
- (c) the risk to human health or the environment from the use of a substance arising from the intrinsic properties specified in Annex XIII(a) is adequately controlled in accordance with Annex I, section 6, and as documented in the applicant's chemical safety report." (EP 2005)

In other words, for use of any such substances to be authorised, industry would need to provide a clear and sound justification in terms of benefits, a description of measures in place to minimise exposure and ensure risks are adequately controlled and, most significantly, confirmation that no suitable alternatives are available. While allowing for authorisation of those uses which are essential, and establishing strict control conditions in such cases, this formulation provides a strong, objective and precautionary approach to ensure that exposures of humans or the environment to all 'substances of very high concern' are avoided wherever possible. By providing just one consistent route to authorisation, the approach is also clear and straightforward.

In contrast, the Council retains two possible routes to authorisation, either by demonstrating simply that the risks from the use are 'adequately controlled' (according to Article 57 paragraph 2 of the Council text) or, if this is not possible, then on the basis of socio-economic benefits and the absence of alternatives (Article 57 paragraph 3). An additional clause under paragraph 2*bis* of the Council text specifies that, for certain groups of 'substances of very high concern', the 'adequate control' route to authorisation cannot be applied:

"2*bis*. Paragraph 2 [the 'adequate control' route to authorisation] shall not apply to:

- (i) substances meeting the criteria in Article 54 (a), (b), (c) [CMRs] and (f) [substances of equivalent concern] for which it is not possible to determine a threshold in accordance with Annex I, section 6.4;
- (ii) substances meeting the criteria in Article 54 (d) [PBTs] and (e) [vPvBs]."

(CEC 2005, bracketed text indicates notes from the author)

Therefore, although paragraph 2*bis* effectively excludes PBTs, vPvBs and so-called 'non-threshold' CMRs from receiving authorisation through the 'adequate control' route,

² European Parliament amendment no. 216

it nevertheless leaves this option open for CMRs and substances of equivalent concern providing it is possible to determine a 'threshold' of exposure to these chemicals below which adverse effects to human health or the environment are not expected.

In effect, under the Council's proposal, companies will be granted authorisations for some uses of chemicals which are carcinogenic, mutagenic, toxic to reproduction or capable of interfering at a fundamental level with the body's chemical signalling and development mechanisms, even if safer alternatives without these properties are already on the market, as long as the resulting exposures of humans and the environment to these chemicals are predicted to fall below certain predetermined thresholds for toxic effects (so-called Derived No Effect Levels, DNELs, or Predicted No Effect Concentrations, PNECs). In those cases the risks will be deemed to be 'adequately controlled'.

While at first sight this may seem to offer an attractive, prudent and entirely objective science-based approach, the setting of thresholds such as DNELs and PNECs depends unavoidably on a number of critical, and frequently untestable, assumptions regarding environmental fates, exposure routes, mechanisms of toxicity and the most sensitive indicators of adverse effects of chemicals.

2 Effect Thresholds: An Objective and Reliable Measure of Safety?

According to the Council text, the manner in which thresholds will be determined is set out in Annex I, section 6.4. In turn, this section refers to two further sections of the same Annex, namely section 1 (addressing human health risks and, therefore, DNELs) and section 3 (addressing environmental risks and, therefore, PNECs).

In both cases, according to the Council proposals, evaluation of any individual substance starts with an assessment of all available information on the hazards presented and their 'dose-response' relationships. Normally, it is stated, "the study or studies giving rise to the highest concern shall be used to establish the Derived No-Effect Levels"; similarly for PNECs. Quite apart from the fact that this might not always be the case (see below), determining which of the toxicological endpoints measured to date represent 'the highest concern' relating to a chemical can be a complex and subjective process. The nature and extent of toxic effects recorded, and the concentrations or doses at which they occur, depend fundamentally on many different factors, including the type of test and conditions selected, the organisms exposed, the timing of exposure and precisely which effects are measured and over what timeframe. Extrapolating to predict effects in other organisms, including humans, adds a further layer of subjectivity.

Take the example of the plasticiser DEHP (bis(2-ethylhexyl) phthalate), classified as 'Toxic to Reproduction, category 2', banned in toys and childcare articles since 2005 but still used in a wide range of other consumer goods. The section of the human health risk assessment addressing toxicokinetics concluded as follows that the generation and excretion of different metabolites depended on a multitude of factors besides species, dose and administration route (including

age, sex, health and nutritional status, and prior exposure history) and that available kinetic data do not explain observed species differences, making extrapolation to humans more difficult still (EU 2001).

Even assuming that it was possible to arrive at a defensible threshold value for the effects of highest concern in an 'average' human, chemical sensitivity and exposure scenarios can vary greatly from one person to another. Indeed, Annex 1 of the Council text proposal recognises this added complexity, noting that "...it may be necessary to identify different DNELs for each relevant human population (e.g., workers, consumers and humans liable to exposure indirectly via the environment) and possibly for certain vulnerable sub-populations (e.g. children, pregnant women) and for different routes of exposure."³

From the very outset, these needs entail very high data requirements, which are costly and time-consuming, and verifiable assumptions if the DNEL thresholds calculated are to be anything other than default values. The situation is similar, if not more complex still, with respect to thresholds for environmental effects (Santillo et al. 1998).

Furthermore, it may be that the effect which should really give rise to the highest concern, because of the nature of the effect and/or the low level of exposure at which it occurs, has simply yet to be discovered or confirmed. Because of the complex nature of the endocrine (hormone) system in wildlife and humans and the fact that it is controlled by very low doses of natural hormones circulating in the body, the toxicology of endocrine disruptors has proven particularly difficult to predict, describe and quantify. Nevertheless, given the range of developmental and metabolic processes which are controlled by hormones, the significance of exposure to chemicals able to interfere with their natural signalling mechanisms cannot be overstated. Serious knowledge gaps remain regarding the effects of endocrine disruptors in humans, compounding the inherent difficulties in establishing cause and effect.

3 Thresholds Depend on What You Look for, and How

Classically, toxicology has focused heavily on lethal effects on test animals of high doses administered over short periods of time. Indeed, such acute tests still form part of the base set of data required for chemical assessment. Invariably, however, sub-lethal effects of acute exposure, as well as both lethal and sub-lethal effects of longer-term (chronic) exposure, are found to occur at doses well below the LD₅₀.

Taking once again the example of the plasticiser DEHP, whereas the LD₅₀ for rats and mice reportedly lies somewhere above the range 10,000–20,000 mg/kg body weight, gross structural damage to the male reproductive tract and complete cessation of sperm production has been reported for the same animals at doses of only 375 mg/kg body weight/day. Moreover, more detailed examination of the spermatogenic Sertoli cells indicates that these can be damaged at doses at least 10 times lower again (with a No Observed Adverse Effect Level at 3.7 mg/kg bw/day) (Poon et al. 1997) while other studies have detected similar effects even at lev-

³ Annex 1, paragraph 1.4.1

els 100 times lower, such that a 'no effect level' simply could not be determined (Arcadi et al. 1998).

Similar trends can be seen with respect to other chemicals which, though still in common use, may be considered to present a high level of concern. For example, the brominated flame retardant decabromodiphenyl ether (BDE-209 or 'deca'), still used in a wide range of polymers, textiles and electronics goods across Europe, has long been characterised as having low acute toxicity (high LD₅₀ value, in excess of 2,000–5,000 mg/kg body weight) (IPCS 1994). Chronic exposures generate toxic effects (especially non-cancer effects) in laboratory animals at lower doses, including reduced red blood cell counts (800 mg/kg bw), resorption of developing foetuses (100 mg/kg bw) and impacts on the liver, kidney and thyroid gland (80 mg/kg bw) (Därnerud 2003). More recently, other studies have shown that 'deca' can cause seemingly irreversible impacts on brain and behavioural development in mice following a single dose as low as 20 mg/kg body weight (Viberg et al. 2003), around 100 times lower than the lowest recorded lethal dose and far below levels which cause any other clinical signs of toxicity. What is more, the scale of the effects observed depends critically on the precise timing of exposure, with the most severe impacts resulting from a single dose delivered on the third day after birth during a sensitive period for brain development.

The apparent ability of 'deca' to degrade in the environment to form less brominated but more bioaccumulative (and possibly even more toxic) BDEs (Stapleton et al. 2004, Söderström et al. 2004) is an added concern, and one which is extremely difficult to address within the DNEL or PNEC threshold concept.

The case of another widely used chemical, the synthetic polycyclic musk fragrance additive HHCB (1,2,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran, otherwise known by its trade name Galaxolide), highlights similar concerns. Although the EU risk assessment for this substance (and for another common polycyclic musk, AHTN or Tonalide) is not yet completed, separate assessments have been carried out under the industry led programme HERA (Human and Environmental Risk Assessment) (HERA 2004). This assessment notes, once again, that the acute toxicity of HHCB is very low (LD₅₀ >3,000 mg/kg body weight). However, a potentially greater concern relating to HHCB, and the polycyclic musks in general, is their endocrine disrupting activity.

The HERA assessment concluded that, whereas HHCB does show some oestrogenicity in human breast cancer cell lines, the effects occur only at relatively high doses (Bitsch et al. 2002). Furthermore, although weak oestrogenicity can be detected *in vitro*, such activity could not be detected using a commonly applied *in vivo* test, the mouse uterotrophic assay (Seinen et al. 1999). On first assessment, this could therefore be taken as an assurance that any endocrine disrupting activity of HHCB would always be well below thresholds for concern.

More recent work, however, suggests a rather different conclusion. Although the ability of HHCB to mimic oestrogen may be relatively weak, it exhibits anti-oestrogenic properties at doses up to 100 times lower (Schreurs et al. 2002).

Furthermore, this effect is not confined to *in vitro* tests but can be detected *in vivo* in zebrafish at similar exposure concentration ranges (Schreurs et al. 2004).

This level of complexity of interaction with just one hormone communication system clearly causes major difficulties for chemical assessment in general, and threshold setting in particular. The possibility remains that polycyclic musks, along with a host of other chemicals in common use, may also mimic or interfere with other hormones in the body, including the male steroid hormones (androgens, such as testosterone) or thyroid hormone. A major EU research programme into androgenic and anti-androgenic activities of various man-made chemicals (under the COMPRENDO initiative) (ENDS Daily 2006) has recently highlighted that these effects may be far more widespread than oestrogenic activity, which has long been the focus of endocrine disruptor research and assessment protocols. They may even be of greater importance in terms of effects at environmentally-relevant concentrations and exposure-levels of chemicals. HHCB, along with the vast majority of other chemicals in use, have never been tested for possible effects on the androgen system, despite the fundamental role this system plays in controlling growth and development in wildlife and humans.

The potential for chemical interference with a diversity of non-reproductive processes, which are also under hormonal control, is even less well accounted for.

4 'There is no Such Thing as a Single Chemical Exposure' (Yang et al. 1998)

Chemical risk assessments almost always consider the consequences of exposure to one chemical at a time. And yet, in reality, we are invariably exposed to complex mixtures of chemicals, from our food and water, in the air, even in the dusts in our homes and offices (Santillo et al. 2003) and in our cars (Gearhart & Posselt 2006). The possibility that chemicals could be interacting in causing adverse effects, which would not be predicted from the properties of the pure chemicals, is very real and yet rarely considered when determining thresholds of exposure and effect.

The presence of any particular chemical in a mixture may impact directly on overall toxicity or the toxicity of other chemicals present, or act to change adsorption or excretion rates, breakdown processes or the bioavailability of other contaminants (Altenburger et al. 2003). In many cases, the resulting effect may be a simple additive one, though both synergistic (greater than additive) and antagonistic (less than additive) interactions are also possible. Even for relatively simple mixtures, effects remain very difficult, if not impossible, to predict with any confidence even where detailed knowledge of the properties of the individual chemicals is available (Zeliger 2003, Komulainen 2004).

In the case of oestrogenic chemicals, for example, it has been noted that "hazard assessments that ignore the possibility of joint action of estrogenic chemicals will almost certainly lead to significant underestimations of risk" (Silva et al. 2002). Though rarely considered at all in a regulatory context, the most commonly applied approach to the problem of mixtures for chemical assessment is the use of generic 'safety factors' to adjust threshold values calculated for in-

dividual components. But as other authors have stressed, "mixture effects are not generic" (Jonker et al. 2005), and may be dependent not only on absolute doses but also on ratios of doses of chemicals in the mixture. In short, there is no way of knowing whether theoretical safety factors will be over- or under-protective in practice.

There are many examples of synergistic effects in chemical mixture toxicology, both in vertebrates (Mori et al. 2006) and invertebrates (Mu and LeBlanc 2004, Schmidt et al. 2005). Nevertheless, even simple additive behaviour can result in significant effects being manifest when all chemicals in a mixture are present at levels which, if taken individually, would ordinarily be insufficient to cause observable effects. In other words, a mixture of chemicals at levels below individually determined effect thresholds can nevertheless show a substantial impact in combination (Altenburger et al. 2003, Zeliger 2003).

In the case of endocrine disruptors, the activity of mixtures can be particularly striking. In vitro studies involving low concentration mixtures of bisphenol-A, PCBs and various other 'weak' oestrogens have revealed 'something from nothing' in terms of oestrogenic activity (Silva et al. 2002), i.e. measured activity from a mixture of 11 xenoestrogens combined and concentrations below their individual NOECs (Rajapakse et al. 2002).

In conclusion, even if it were possible to arrive at robust, reliable and sufficiently protective threshold values for individual chemical exposures, it is unlikely that these would provide effective protection in the real world, given that we are constantly exposed to complex and ever-changing mixtures in practice. Robust approaches to risk assessment for chemical mixtures seem likely to remain elusive (Borgert 2004), potentially leading to serious underestimations of risk in some cases.

5 An Alternative Approach: Precaution and Substitution

Taking into account all the inherent problems and uncertainties discussed above, it must surely be a more prudent, precautionary and defensible approach to avoid the use of and, therefore, exposure to all CMRs or chemicals of equivalent concern (including endocrine disruptors) wherever and whenever possible. This is not to say that all proposed uses should automatically be prohibited from authorisation under REACH, but rather that such uses should *only* be permitted where no safer alternatives are currently available, the benefits are unquestionable and the risks can be properly controlled.

In essence, this is the approach adopted by the Parliament in its first reading (see above). It provides for essential and irreplaceable uses of 'substances of very high concern', be they PBTs, vPvBs, CMRs or chemicals of equivalent concern, to be authorised through one logical and consistent route rather than placing reliance on estimations of effect thresholds and exposures. Under the Parliament's proposals, the existence of a suitable safer alternative, be it a different chemical, material, technology or other alternative, would be sufficient in itself for an authorisation for that use to be refused (recognising that, in certain cases, temporary authorisation may nevertheless be necessary in order to give time for such substitutes to be put fully into place).

Furthermore, the approach adopted by the Parliament takes far greater account of the propensity for new, safer and more sustainable solutions to emerge over time. Indeed, by requiring that all authorisations issued are subject not only to a strict time limit (not exceeding 5 years) but also to "review periods and the presentation of substitution plans"⁴, the Parliament's approach would ensure that REACH would act as a strong driver for substitution of the most hazardous chemicals currently in use with safer alternatives. Current absence of a workable alternative would become an incentive to develop one rather than a justification for 'business as usual' and thus a strong driver for sustainable innovation, one of the key elements of the EU's Lisbon Agenda. This approach would also be consistent with the direction given to the EU by the Ministerial Meeting of the OSPAR Commission in 2003 and, indeed, consistent with the objective of OSPAR's Hazardous Substances Strategy to stop releases of all hazardous substances to the marine environment by the year 2020 (the 'one generation' goal).⁵

Taking some of the specific chemical examples referred to above⁶, it is clear that the manner in which they would be addressed under the Parliament and Council proposals, and the consequences for protection of the environment and human health, could differ quite markedly. Whether for the category 2 reproductive toxicant DEHP, the possibly neurotoxic decabromodiphenyl ether ('deca') or the potential endocrine disruptor HHCB, alternatives have been available and on the market for some time. Case study examples of substitution in action are available elsewhere (Greenpeace 2005).

It will, of course, remain vital to ensure that one problem chemical is not simply replaced with another. Hence replacing DEHP with other toxic phthalates or poorly assessed alternative plasticisers, replacing decabromodiphenyl ether with decabromodiphenyl ethane (Kierkegaard et al. 2004) or other brominated or chlorinated flame retardants, or even replacing polycyclic musks like HHCB with largely unassessed macrocyclic musks before there is confirmation of their

⁴ Parliament amendment 235 to Article 57, paragraph 6

⁵ The 1992 OSPAR Convention (<http://www.ospar.org>), which aims to protect the marine environment of the North East Atlantic region and includes many European countries and the European Commission as Contracting Parties, established in 1998 a strategy to address hazardous substances which requires, *inter alia*, the cessation of discharges, emissions and losses of hazardous substances by 2020 (i.e. within one generation). Precaution and substitution are two guiding principles of the Hazardous Substances Strategy. In 2003, recognising the potential for the then newly developing EU chemicals policy to contribute to OSPAR's objectives, OSPAR Ministers concluded:

"In the further development of the EC Chemicals policy we encourage the European Community:

- a. to take full account of the need to protect the marine environment;*
- b. to take account of our commitments to move towards the cessation of emission, discharges and losses of hazardous substances;*
- c. to promote the substitution of hazardous substances with safer alternatives, including promoting and facilitating the development of such alternatives where they do not currently exist*
- d. to ensure that purchasers and consumers are provided with information on hazardous substances in goods, to help reduce the risks from them."*

⁶ The specific cases of these three chemicals are highlighted here as an illustration of a wider concern. Until it becomes clear precisely which 'substances of very high concern' will ultimately fall into the category for which the Council envisages that thresholds may be set (and, therefore, the 'adequate control' route applied), a more exhaustive analysis of the potential consequences is not possible.

greater safety, would all be unwise decisions. What is clear, however, is that a requirement to substitute whenever possible does not circumvent the difficult process of identifying the most appropriate alternatives. It seems inevitable that methods to guide substitution decisions will need to be developed further, and that case-by-case considerations will be essential to account for technological complexities, performance needs and to avoid oversimplification. What can be established at the outset, however, is that any proposed substitute should, at the very least, not be another 'substance of very high concern'.

Furthermore, it is likely that in many cases, the most suitable alternative will not be a simple 'drop-in' chemical replacement, e.g.:

- i. alternatives to continued widespread use of DEHP include use of alternative polymers or other materials which confer flexibility on the product without the need for mobile and leachable chemical additives;
- ii. whereas less hazardous but equally effective non-halogenated alternatives to brominated flame retardants have long been available (Lassen et al. 1999), albeit often at some additional cost to manufacturers, non-combustible materials and novel product designs undoubtedly also have a role to play (Santillo and Johnston 2003).
- iii. in the case of polycyclic musks, while there are many natural fragrances which could provide replacements, their inherent greater safety should not be assumed, and it is vital therefore to reconsider the need for, and benefits of, such widespread fragrance use in a diversity of consumer products or whether they can simply be omitted.

In short, it is common sense that any unnecessary use of chemicals, and the exposure it entails, should be avoided.

According to the Parliament's formulation, it would seem reasonable, therefore, that few if any continued uses of these potential 'substances of very high concern' would receive authorisations.

In contrast, it is feasible under the Council's proposals that all three chemicals – DEHP, 'deca' and HCB – would be regulated according to a series of exposure scenario-specific effect thresholds, such that their widespread use and release to the environment, though entirely avoidable, would nevertheless be allowed to continue. In the long run, this cannot be a sustainable or precautionary approach.

Moreover, faced with the inevitable limitations to time, technical expertise and financial resources, it may be better to invest more in the identification, development and implementation of safer and more sustainable alternatives, including clear and timed substitution plans where necessary, and rather less in the assessment of risks, definition of thresholds and determination and monitoring of 'safe' levels of exposure for substances which already present very high concerns and which could be readily replaced.

6 Conclusions

We stand at a critical decision point for the future of our environment and for the health and security of generations to come. For the EU to provide the high level of protection to which it aspires, it will be essential that the decisions made

in finalizing REACH will render it capable of addressing and ultimately reversing the potentially devastating trends in environmental and human health currently being observed.

The Council of Europe's current proposed approach for the management of CMR and endocrine disrupting chemicals threatens to undermine this protective aspiration. Rather than providing an objective guarantee of safe chemical exposures, effect thresholds are frequently highly theoretical, based on a limited understanding of the potential for toxic effects at low doses and, therefore, may provide little more than a false sense of security.

Furthermore, as toxicology has evolved, the detection of adverse impacts of chemicals at lower and lower doses has been a consistent trend. As illustrated by the examples above, levels previously thought safe have time and again been proven otherwise.

Two important lessons can be drawn from these examples. Firstly, the fact that no effect is observed in any particular toxicity test cannot be taken to imply that the chemical has no adverse effect of any kind on the test organism; it may simply be that the test conditions used do not allow us to observe the effects, either because they are not sensitive enough or because we are simply looking for the wrong type of effect.

Secondly, it follows that the effect thresholds determined from toxicity tests (be they DNELs or PNECs) will also depend on what we measure and how, and the assumption that this is the most sensitive and/or relevant indicator for chemical safety assessment. When we are dealing with chemicals which are carcinogenic, mutagenic, toxic to reproduction or capable of disturbing the endocrine system, this seems to be an unwise and unnecessary risk to take.

The fact that we are exposed constantly to chemical mixtures adds an additional layer of complexity and uncertainty to that already arising from the difficulties of setting thresholds for individual chemical exposure.

Taken together with the Council's recognition (noted above) that thresholds may also differ depending on the nature and route of exposure, we are left with a seemingly unmanageable situation. Certainly it is one in which reliance on Derived No Effect Levels (DNELs) and Predicted No Effect Concentrations (PNECs) to confer protection is an incautious and highly questionable approach.

In contrast, if drafted correctly, incorporating a single route to authorisation and a requirement for substitution, wherever possible, for 'substances of very high concern', REACH could act not only to protect our health and environment for the future but also as a driver for innovation and positive change within the European chemical industry with benefits to all levels of society.

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