

Report



**Friends of
the Earth**

Crisis in Chemicals *Update*

March 2002

In May 2000 Friends of the Earth warned, in the *Crisis in Chemicals* report, that the 'Biomedical Revolution' would have a substantial impact on the regulation and use of chemicals.

This update looks at what has happened in the two years since the report was published, and whether the warnings given in the report are being born out by the research.

The full *Crisis in Chemicals* (CIC) report can be purchased from Friends of the Earth, or downloaded free:

www.foe.co.uk/campaigns/safer_chemicals/resource/experts.html

1. Executive Summary

- Scientific research on the application of biomedical revolution techniques to toxicology is proceeding rapidly, as predicted in the *Crisis in Chemicals* report.
- Particular progress is being made in the application of expression profiling – a technique that can provide an in depth look at what's going on in cells following exposure to a chemical.
- Research is already providing an insight into the mechanisms behind endocrine disruption – and new arrays have been manufactured that are now being used to discover a huge amount of information about currently understood, and still to be identified, endocrine disrupters.
- Scientists are also beginning to find significant individual genetic susceptibilities – with individuals claiming ill health from the petrol

additive MTBE and organophosphate sheep dips being found to be more likely to have less effective breakdown enzymes.

- A new regulatory system in Europe is being created – but the current proposals will not be sufficient to cope with the expected developments in science. More openness is needed, as is more precautionary action on chemicals that accumulate in our bodies or are endocrine disrupters.
- The chemical industry is still pushing for a secretive, non-precautionary system, whilst many high street retailers and downstream users still seem unaware of the problems posed by the chemicals they are using and selling. Industry, including retailers, is leaving itself open to loss of confidence and an increasing number of liability cases as it becomes easier to identify illnesses caused by specific chemicals.

2. Introduction

We are exposed to industrial chemicals all the time, in our food, in household products and as general contaminants of our environment.

One might think that the chemicals we are exposed to have been checked to ensure they will not adversely impact on our health. In reality we know little about the safety of most chemicals. The latest data from the European Chemicals Bureau, responsible for collating information on chemicals in the EU, has shown that only 14% of the chemicals used in high volumes in the EU have a full minimum set of safety data publicly available, whilst 21% have no publicly available safety data at all [1].

There are serious concerns about what these chemicals may be doing to our health. Of particular concern are the effects that chemicals may be having during the development of our bodies, when we are in the womb and when we are children. Several childhood and other cancers, are increasing in incidence, as is asthma.

2.1 Difficult to link a chemical to a health impact

A major problem with linking exposure to a particular chemical, or anything else, to a particular illness is the multiplicity of other factors which could be affecting the incidence of the illness. Occasionally, making a link is easy, for example if the exposure leads to a unique illness, as for example with asbestos. However, even with links that should be easy to make, such as that between lung cancer and smoking, years of research (and exposure to the chemical) may be required. Even for chemicals known to be hazardous it is virtually impossible for someone to prove that they have been harmed by a particular chemical.

More complex problems, like changes in IQ, behaviour or performance of the immune system, are even more difficult to link to exposure to specific chemicals. Health impacts associated with chemicals may include cancers such as testicular and breast cancer, reduction in sperm counts, damage to brain development and harm to the immune system.

2.2 The coming revolution in understanding

The '*Crisis in Chemicals*' report argues that, over the next 10 years, a revolution in our understanding of the human body will provide new ways of understanding the impacts of chemicals on the body. The human genome project and the developments that follow on from it, the 'biomedical revolution', will vastly improve our understanding of how the body works and the impacts of chemical exposures on it, including:

- Increased understanding of how the body works will make it easier to detect the effects of chemicals – eg if you can understand and measure the performance of the immune system, then you can measure damage to it.
- Individuals vary in their ability to break down chemicals, and in how much they respond to the toxicity of chemicals. Much of this variability is genetically determined, but currently we know few details. As susceptibilities to individual chemicals are discovered, people will be able to be screened easily and cheaply, and discover if they are among the susceptible groups.
- Faster, more comprehensive methods of measuring the pattern of toxic response caused by well known chemicals will enable rapid identification of the toxic effects of new or less well understood chemicals.

There is also huge potential for these new methods to be done *in vitro* (without animals), thus creating more rapid, cheaper and more humane safety assessment of chemicals.

2.3 Why is this important?

As this research is published, it will be rapidly communicated, resulting in many impacts, including:

- sensitive individuals will want to avoid specific chemicals;
- the public – and downstream users such as retailers – will want to avoid chemicals that have been newly identified as hazardous;
- affected individuals will want redress from the industry making or emitting the chemicals of concern, and from those involved in selling products containing the relevant chemicals;
- the public will demand that regulators protect them.

Crisis in Chemicals was welcomed by the UK Government, who said “it highlights the possible implications of emerging research into the genetic susceptibility of individuals to chemicals, and rightly points out that this research will eventually bring a better understanding of the mechanisms of chemical toxicity” [2].

2.4 An update

The rest of this update examines what progress has been made – both on a policy and scientific level – since May 2000. Is scientific research happening in accordance with the predictions in *Crisis in Chemicals*? How are the regulators and industry responding to the biomedical revolution?

3. Research news

3.1 Research is stepped up around the world

Governments across the world are investing in biomedical revolution-related research, focussing both on general public health and on toxicology and environmental health. The USA is particularly prominent on the latter, and a new National Centre for Toxicogenomics was formerly established in September 2000 [3]. This is only one of the projects created by the US Government's National Institute for Environmental Health Sciences (NIEHS), which also funds the Environmental Genome project, and whose journal *Environmental Health Perspectives* has had a number of major features on the issue, eg in January 2001 [4-6]. Another NIEHS study (joint with the US Environmental Protection Agency) is investigating the role of genetic susceptibility and chemical exposures in autism [7].

Other scientific bodies in the US have also been promoting the importance of these new techniques, with the influential National Research Council calling for the use of human genome related

techniques to investigate the relationship between birth defects and chemicals [8].

Meanwhile, in the UK, there has been considerable debate over the development of a large genetics database, to be organised by the Medical Research Council and the Wellcome Trust, which is intended to contain samples from up to 500,000 volunteers. The development of this database, now known as 'BioBank UK' [9], has been supported in a report from the House of Lords Select Committee on Science and Technology [10].

Private consortia are also investing in these new technologies. One of the most interesting of these is the Myriad consortium, which intends to spend up to £350m to analyse every protein in the body – within 3 years (the project was announced in April 2001 - [11]).

3.2 Routine medical application comes closer

The UK Government has announced a £30 million package of spending “to help bring the genetics revolution into everyday medical practice” [12]. This spending is intended to lead to a doubling in the number of consultants specialising in genetics and genetic counsellors by 2006.

The impact of genetic makeup on adverse reactions to pharmaceuticals is becoming clearer, with one recent review proposing that 10-20% of adverse drug reactions and deaths could be prevented by predictive genotyping [13]. The significance of this figure can be seen when the health impact of adverse drug reactions is realised – it is estimated that 7.5% of hospital admissions in the UK are due to such reactions [13].

The Crisis in Chemicals report suggested that the impacts of the biomedical revolution would be felt over the next 5-10 years. A similar timescale has been proposed for medical application in a review in September 2001 in the British Medical Journal [14], which concluded:

“The increased diagnostic and prognostic information provided by microarrays should assure their entry into clinical practice in specialist centres within 3-5 years and in most large hospitals with 5-10 years”

One area where rapid progress is already being made is in the application of expression profiling to the diagnosis and treatment of cancer. For example, it is clear that expression profiling is able to distinguish different types of breast cancer, which is likely to have a major impact on the way treatments are selected in the future [15, 16].

3.3 Researchers are optimistic

As can be seen from the brief examination of research findings below, scientists are very optimistic about the effectiveness of these new techniques.

Whilst acknowledging that care must be taken to ensure that results are reproducible, comparable and meaningful, it is clear that the general belief is that techniques such as expression profiling (Box 1) are already revolutionising toxicology.

There is less rapid progress on understanding individual susceptibilities, partly because published research is still using techniques that can only examine variations in a few genes at once, rather than using microarray techniques to examine many genes at once (Box 1). This is expected to change over the next year or two as the information from the human genome project is used to construct powerful microarrays.

3.4 The chemical industry tries to get its retaliation in early

The trade association for a large part of the UK chemical industry, the Chemical Industry Association, attempted to dismiss the Crisis in Chemicals report. In their Annual Report for the year 2000 they talk about ‘the contrived nature of (Friends of the Earth’s) link between the Human Genome Project and a call for further regulation of the industry’.

In contrast, other parts of the chemical industry have been waking up to the regulatory impacts of the biomedical revolution. For example, the trade association for the European chemical industry, CEFIC, has added a genomics element to their ‘Long Range Research Initiative’. At a talk at a conference in 2001, the director of this initiative made the following points [18]:

- “Molecular Biology Revolution is here”

Box 1: Microarrays

A DNA microarray or 'DNA chip' is a solid support spotted with a grid of small spots of either short cDNA sequences or oligonucleotides. They have two major applications [17]:

(i) Expression profiling

The microarray is spotted with the DNA sequences of several thousand genes of interest. A sample is taken from the cells of interest, then the mRNA is extracted. The mRNA is then added to the chip, and those mRNA sequences corresponding to DNA sequences of genes on the chip will bind to the relevant spots. The amount of RNA bound to each spot is measured, thus giving a measurement of what genes are being transcribed and translated by the cell at that moment.

(ii) Screening of DNA variation

These chips use oligonucleotides which include a range of sequences that are known for particular variations in genes. The DNA of an individual is then processed and added to the chip, and the binding of the DNA shows which sequences are present in that individual.

- “Genomic, proteomic, and metabonomic technologies expanding faster than our ability to interpret the results in risk terms”
- “High potential for gene expression data to be interpreted and applied prematurely”
- “Concern that....as data are developed, there will be the desire to apply it to the risk assessment process prematurely”

In addition, the US-based Chemical Industry Institute of Toxicology (recently rebranded ‘CIIT Centres for Health Research: Research to Benefit Human Health’) has created a ‘Centre for integrated genomics’ to investigate individual susceptibilities and other aspects of the use of genomic techniques in toxicology [19].

The chemical industry is clearly becoming aware of the potential impact of these technologies on confidence in, and regulation of, their chemicals. They are already preparing the ground for arguing that ‘this new data is not robust enough to regulate with’ or ‘this research doesn’t prove that our product is dangerous’, arguments that the industry constantly use to avoid, or at least delay, regulation of their chemicals, even when there is substantial evidence that they are a problem.

However, the industry themselves are investing in these technologies for their own use, particularly in the pharmaceutical sector. As outlined below (‘Development of new arrays’ in Section 2.1), industry scientists from Syngenta (formerly Astra-Zeneca – and even earlier part of ICI) are saying that expression profiling is rapidly becoming a standard technique in toxicology.

Those offering training to toxicologists and chemists are also realising the importance of the biomedical revolution. For example, the training organisation ETAF offered a two day course in March 2001 on ‘Use of genomics and proteomics in toxicology and pharmacology’. Their introduction to this training course emphasised the importance of the field [20]:

“The fields of toxicology and pharmacology are presently undergoing a revolutionary change as a consequence of remarkable achievements in our ability to understand and measure changes in the expression of both genes and proteins at the genome wide level.....identification of new biomarkers to help categorise exposure to toxic compounds and their potential effects in populations of humans and other organisms....Of particular interest is the option to examine the molecular background of differences in susceptibility to certain toxic chemical groups, known to exist among individuals”

4. Scientific Progress

4.1 Expression profiling - the application to toxicology begins

Since the publication of *Crisis in Chemicals* a growing number of papers have been published

where expression profiling is being used to examine both human and environmental toxicology. Table 1 gives a brief description of some of the recent research in this area, and a number of the studies are discussed in more depth below.

Investigating the impact of chemicals on the liver

As Table 1 shows, many researchers have been examining the effect of chemicals on the liver by using gene expression arrays. What is claimed to be the first research “to describe the construction and use of a transcript profile database that begins to distinguish chemicals from different mode of action classes” [21] was published in December 2000 [22]. It was found that a 250 gene array could discriminate between those chemicals with DNA-damaging toxicity and those that were anti-inflammatory compounds. However, it was necessary to use several methods of analysing the data to identify those that best discriminated between the different modes of toxicity.

Identifying and classifying allergenic chemicals

Chemicals are well known causes of allergy, with many chemicals having been identified as causing allergic responses such as contact dermatitis and asthma. However, these responses are still not well understood, so researchers have started using gene arrays to both improve understanding of what is happening at a molecular level during allergic responses, and to develop a system that could predict which chemicals are allergenic [23].

Three different chemicals, toluene diisocyanate, oxazolone and nonanoic acid, each known to cause allergic effects through different mechanisms, were applied to the ears of rats, then lymph nodes were examined with a 6,519 gene array. Genes that showed interesting responses in the array were also amplified for further evaluation. The study showed that there were many differences in expression between the three chemicals, thus it contributed to the future development of a method that could identify different sorts of allergenic chemicals.

Understanding the effects of diesel exhaust particles on the lung

It is well known that high levels of particulate (PM10) air pollution are strongly associated with increased hospital admissions and deaths, but the precise nature of the toxic effects of particulates is still not understood. Researchers at Cardiff University [24] examined the effect of diesel exhaust particles on rat lung. Earlier studies had tended to focus on higher exposure than would be typical for a person in a city, and have not examined in detail the changes happening in the lung cells themselves.

These researchers used a macroarray with 207 rat stress genes to examine the effects of diesel particulates on rat lung. The study showed that on exposure to diesel exhaust particulates, seven out of the 207 genes had increased expression, one had reduced and two were switched on. This information

improves our understanding of the toxic effects of particulates, and the authors were able to conclude that the results were consistent with current understanding of the toxicology of particulates, and they proposed that more research could be done to examine the impacts of different types of particulate matter.

Understanding the response of plants to toxic stress

It's not only humans and animals that are affected by pollution. It's well known that ground level ozone pollution (caused largely by traffic pollution, but made worse by other sources of volatile organic hydrocarbons) damages plants, and generally this

Table 1: Recent toxicology research using expression profiling

Aim of research	Year	Results
Effect of around 100 liver toxins on human liver cells <i>in vitro</i> .	2000 [22]	Managed to distinguish between the modes of action of different chemicals - see text.
Effects on people living in Guizhou, China, of chronic exposure to high levels of arsenic, by analysing gene expression in the liver.	2001 [25]	Established the key genes whose expression changes on chronic exposure to arsenic, potentially improving understanding and treatment of arsenic toxicity in humans.
Changes in human liver cell gene expression on exposure to dioxin <i>in vitro</i> .	2001 [26]	Found that dioxin exposure led to changes in expression of a large number of genes.
Effect of lead on cells from rat blood-brain barrier (astrocytes) <i>in vitro</i> .	2001 [27]	Established 'signature' for lead on the microarray, and identified a new molecular target for lead in the brain.
Impact of diesel exhaust particulates on rats, through examining lung tissue.	2001 [24]	Discovered which genes responded to particulates, opening up the opportunity to improve our understanding of particulate toxicity - see text.
Effect of ozone stress on the <i>Arabidopsis</i> plant.	2002 [28]	Identified gene expression patterns which could distinguish between ozone, drought and wounding - see text.
Effects of exposure to bi(n-butyl) phthalate (DBP) in the womb on foetal rat testes	2001 [29]	DBP is a known endocrine disrupter, but its mechanism of action has been uncertain. This study suggests it's at least partly due to decreased testosterone synthesis.
Effect of three irritant and sensitising chemicals on mice, analysing gene expression in lymph nodes.	2001 [23]	The array was able to distinguish between chemicals which were known to use three different modes of action – see text.
Use of the roundworm <i>Caenorhabditis elegans</i> as a monitor for endocrine disrupting properties.	2001 [30]	Gene expression patterns distinguishing between progesterone, oestrogen and testosterone were observed.
Changes in expression of brain proteins when Snapping Turtles are exposed to the oestrogenic alkylphenol octylphenol.	2002 [31]	Low levels of octylphenol influence the expression of genes involved in neuronal development.
Impacts of exposure to octylphenol and UV-B radiation in the Leopard Frog, examining gene expression in the hypothalamus.	2002 [32]	Exposure of tadpoles to both octylphenol and UV-B radiation led to changes in development. Examination of gene expression showed that octylphenol alone led to changes in expression of important hypothalamic genes.
Toxic responses in liver and kidney cells from mice exposed to 10 toxins from five classes (polyaromatic hydrocarbons, DNA alkylators, peroxisome proliferators, heavy metals and oxidative stressors.)	2001 [33]	A 260 gene array was used to successfully distinguish between chemicals (such as benzo(a)pyrene and carbon tetrachloride) in the five classes of toxicity.
Toxic responses in liver cells from mice exposed to Cadmium chloride, Benzo(a)pyrene and Trichloroethylene.	2001 [34]	<i>"Microarray analysis with a highly focussed set of genes is capable of discriminating between different classes of toxicants"</i>
Effect of 24 liver toxins from five classes on mice, analysing gene expression in liver cells.	2001 [35]	<i>"...provided an estimated 100% predictive accuracy...Expansion of this approach to additional chemicals of regulatory concern could serve as an important screening step in a new era of toxicological testing"</i>
Effect of six liver toxins on rats, analysing gene expression in liver cells.	2001 [36]	<i>"This study supports the use of gene-expression profiling to determine or predict toxic liver effects"</i>
Effect of 15 liver toxins on rats, analysing gene expression in liver cells.	2001 [37]	<i>"Overall, the results suggest that microarray assays may prove to be a highly sensitive technique for... the classification of environmental toxins"</i>
Effect of 15 liver toxins on rat liver cells <i>in vitro</i> .	2001 [38]	<i>"...reasonable agreement between our in vitro observations.. and in vivo responses... suggesting that in vitro studies would have been predictive for the in vivo toxicity"</i>

damage has been measured by estimating leaf injury. However, Japanese researchers have now used a small microarray with just 12 genes to examine the effects of ozone, drought and wounding on *Arabidopsis thaliana* plants [28]. Even with only 12 genes, the researchers were able to detect and discriminate between these three stresses. This research provides a method of measuring the harmful impact of air pollution on plants far more effectively, which may well have regulatory impacts. In addition, it is possible that similar research may identify new chemical air, water, or soil pollutants that are affecting plant health.

Development of new arrays

There are many new expression arrays being developed, with some of them designed to examine the effects of toxicants on particular tissues. For example:

- Scientists from the pharmaceutical company Syngenta (formerly Astra-Zeneca) have developed the ToxBlot II array, which includes 13,000 human genes of relevance to toxicology [39]. They are now using this array to investigate a wide range of toxic effects, including endocrine disruption. They also state "*The application of transcript profiling to toxicology is rapidly become (sic) a standard approach in molecular toxicology*".
- Research part-funded by the US Environmental Protection Agency, as part of the US Environmental Protection Agency MicroArray Consortium, has led to the development of two arrays for investigating testicular toxicology, one of 950 mouse genes and one of 960 human genes [40]. In both cases the genes have been selected to be relevant to testicular tissue, and initial results with a known testicular toxicant have shown that the array generates useful data.
- Another research project has examined the production of a flow-through array, with the intention of using it as part of a system to investigate the toxicity of environmental samples such as contaminated soils [41].

The likely impact of the biomedical revolution on the endocrine disruption debate

Due to the complexity of the endocrine (hormonal) system, it presents an ideal target for expression profiling. Research in this area is speeding up, with Syngenta scientists using a 600 element microarray to compare expression profiles of MCF7 (human breast cancer) cells exposed to bisphenol A and other oestrogens [39] - note though that this paper provides no detailed results.

In addition, Table 1 includes a number of early applications of expression profiling to endocrine disruption – for example the use of the heavily researched (and fully DNA sequenced [42]) nematode worm *Caenorhabditis elegans* to screen for endocrine disrupters, and work at the CIIT on the

endocrine disruption mechanism of di(n-butyl) phthalate.

A European Commission workshop on endocrine disrupters in June 2001 concluded that the biomedical revolution would provide powerful new tools for investigating endocrine disruption [43]:

"Greater use should be made of genomics..., transcript profiling..., proteomics..., and metabonomics... They could provide powerful tools... to target testing, address low dose effects, mixtures and decrease the number of test animals used... facilitating more rapid screens for effects."

Similar conclusions were reached at an International Symposium on endocrine disruption in Japan [44], which revealed a growing consensus that endocrine disrupters can be active at low dose levels. Also highlighted was the large genetic variability, up to 1,000-fold, which exists in animal responses to hormone disrupting chemicals.

4.2 Increased understanding of genetic susceptibility

In contrast to the situation with expression profiling, studies published recently on genetic susceptibility are not yet using new techniques such as DNA arrays. As a result, the acceleration of discovery in this area has not yet begun, though there is a steady stream of publications (See Table 2). In the interests of brevity, this table does not include a full explanation of the genes discussed – for more background refer to pages 22-31 of the *Crisis in Chemicals* report.

One area to which increased attention is being paid is the examination of how genetic susceptibility will impact on the way we evaluate and regulate exposures of populations to chemicals.

A transformation in epidemiology?

Epidemiology is the standard technique used to examine relationships between health of a population and exposures to chemicals or other substances, for example the studies that were done to show that smoking causes lung cancer. Epidemiology is, however, quite a blunt tool and it is often very difficult to isolate an effect due to an exposure from all the other elements that impact on people's health. Another significant element that is usually ignored in epidemiology is the issue of individual susceptibilities. An analysis by US scientists has shown that such susceptibilities can lead to epidemiology giving falsely reassuring results [45]. This analysis re-examines an epidemiological investigation of the possible impacts of methylmercury exposure on development in children on the Seychelles.

The original investigation used a linear dose-response model, and could not detect a significant impact of methylmercury on the children. However, there is strong evidence of considerable individual variability in response to mercury, so the new

analysis looked at what would happen if it was assumed that 5% or 10% of the population were more susceptible than the rest. They concluded that even with a large sample (700 children), linear regression ‘did not reliably detect a dose-response relationship for most scenarios when sensitives were 5% and from some scenarios when sensitives were 10% of the total’.

Put simply, this analysis showed that epidemiological studies will usually not pick up an effect if it’s only a small percentage of the population that is susceptible to this effect. In the future, it should be possible to identify the susceptible individuals, and analyse them separately.

This could result in previously-negative epidemiological studies becoming positive for a group of the population. It’s worth noting that such analysis could be retrospective, as long as DNA samples could be obtained from participants in the earlier study. This could have very interesting implications for legal actions.

The influence of individual susceptibilities on exposure standards

As there has been limited progress in identifying individual susceptibilities since *Crisis in Chemicals*, there hasn’t been much change in impact on regulatory systems. However, some studies are being carried out, for example Swedish scientists have

Table 2: A selection of recent research examining variations in susceptibility

Aim of research	Year	Results (see pages 22 – 31 of CIC for more explanation of terms)
Comparison of Paraoxonase (p26 CIC) polymorphisms in farmers who attribute ill health to sheep dip with farmers who had no health effects.	2002 [46]	Paraoxonase is an enzyme involved in breaking down organophosphates, chemicals which have been used in sheep dip. This study found that farmers attributing ill health to sheep dip were more likely to have Paraoxonase enzymes which were less effective on the organophosphate contained in sheep dip compared to those that were healthy.
Examination of detoxification enzymes in people who get leukaemia as a result of anti-cancer treatment.	2001 [47]	Patients with at least one valine at codon 105 of GSTP1 were more likely to develop chemotherapy-induced leukaemia, probably because they were less able to detoxify the chemotherapy drugs.
Examination of variability in enzymes for detoxification of MTBE in individuals identifying themselves as ‘susceptible’.	2001 [48]	Found that CYP2A6 was an important enzymes for MTBE breakdown, and identified that some sensitive individuals had a mutation which completely inactivated this enzyme.
Profile of xenobiotic metabolism enzymes in survivors of the Spanish ‘Toxic Oil Syndrome’, which killed more than 300 people	2001 [49]	In a comparison of people who reported symptoms with others who didn’t but were in the same families or lived in the same areas, those with symptoms were more likely to have defects in the NAT2 detoxification gene.
Investigation of a type of infant leukaemia (due to fusions in the MLL gene) and its links with detoxification enzymes.	1999 [50]	Discovered a strong link between this leukaemia and low or no activity in a quinone detoxification enzyme, HQO1. (research not included in CIC)
Examination of the link between coronary heart disease in men who had died suddenly, and polymorphism of the human α oestrogen receptor.	2000 [51]	Men with longer dinucleotide repeats in the regulatory region of the oestrogen receptor were more likely to have myocardial infarction.
Examining the relationship between detoxifying glutathione S-transferases and early onset prostate cancer.	2001 [52]	People with one or two valines at position 105 of GSTP1 (p24 CIC) were more likely to get early onset prostate cancer.
Effect of polymorphisms on the number of haemoglobin adducts found in workers exposed to acrylonitrile.	2001 [53]	People with one GSTP1 polymorphism had higher levels of an acrylonitrile-specific haemoglobin adduct, whilst a GSTT1 polymorphism affected the level of adducts caused by endogenous ethylene oxide.
The impact of genetic polymorphisms on the birth weight of the offspring of mothers who smoke.	2002 [54]	Mothers who had a combination of two polymorphisms – CYP1A1 Aa & aa and GSTT1 absent – were more likely to have low birth weight children.
The effect of polymorphisms in the vitamin D receptor and the ALAD genes (p31 CIC) on lead dose and, blood pressure and hypertension.	2001 [55]	A polymorphisms of the vitamin D receptor was significantly associated with blood lead, tibia lead, blood pressure and hypertension.
Examination of the impact of ALAD polymorphisms on lead distribution in the blood and bone.	2001 [56]	ALAD polymorphism did appear to have an impact on the way lead was distributed amongst different bone types and the blood.

examined the impact that individual variability in metabolism of dichloromethane has on cancer risk from this chemical [57]. They estimate that this variability means that susceptible individuals are not adequately protected by the uncertainty factor normally used to derive exposure standards.

5. Is the regulatory system prepared?

The *Crisis in Chemicals* report proposed that the advances in science, described in this briefing, provide a very real threat to the ineffective and secretive system currently regulating the production and use of chemicals (for more detail, see Sections 4-6 of the full report).

In the period since the report was published there has been continued progress towards the creation of a new regulatory system for chemicals in Europe – but will this new system be designed to cope with the biomedical revolution?

5.1 The new EU chemicals policy - progress so far

The debate is on about how to replace the current system - tougher regulation or devolve responsibility to industry? As the president of the European Chemical Industry Association (CEFIC), said in December 2000, this review is a '*once in a lifetime opportunity*' to change the regulatory system [58].

On February 13th 2001 the European Commission finally published, following intense debate, its White Paper on a new chemicals policy [59]. Margot Wallström, head of the European Commission's Environment Department, had earlier complained that "*Industry are lobbying very hard against a new chemicals policy*" [60], and in Friends of the Earth's view the final White Paper showed that the chemical industry had won many elements of this round of the debate [61]. Some of the key features of the new 'Registration, Evaluation and Authorisation of Chemicals' or 'REACH' system include:

- An obligation to deliver safety data on all chemicals by deadlines (Registration). For higher volume chemicals this data will be evaluated by Member State experts in association with an central co-ordinating body – this evaluation may then lead to risk reduction or authorisation.
- Chemicals of 'very high concern' be phased out, except for Authorised uses, where industry has been able to argue that there is no safer alternative, and a societal need for the chemical.

A particular issue of debate is that the White Paper does not define chemicals that accumulate in the body – those that are very persistent and very bioaccumulative (vPvB) or persistent, bioaccumulative and toxic (PBT) – as 'very high concern', though this was in an earlier DG Environment draft [62].

In June, Environment Council (the Environment Ministers of the Member States) agreed 'Conclusions' on the White Paper [63], strengthening it, adding back in controls on chemicals that accumulate in our bodies, and controls on chemicals in imports.

The White Paper was then examined by the Environment and Industry Committees of the European Parliament, with the Environment Committee voting to strengthen it. However, after 'voracious' chemical industry lobbying, the full Parliament weakened this report on November 15th 2001. In particular, the MEPs voted to allow continued use of chemicals that accumulate in our bodies - and this vote was carried because most UK Labour MEPs voted for continued contamination, despite the fact the UK Government view (expressed at June's Environment Council) was that such chemicals should be restricted.

5.2 What happens next?

Following on from a series of technical working groups (with involvement from a wide variety of stakeholders), the Commission is now drafting new legislation, which is due to be published in summer 2002. This draft legislation will then be debated by MEPs and by Environment Ministers. There will probably be at least two more years of debate before a new law is in place.

5.3 The policies promoted by environmental groups

In 1999 Friends of the Earth and WWF began a discussion with environment and consumer groups across Europe to formulate a common set of policies for this review. The agreed policies, now known as the '**Copenhagen Charter**', are also supported by the EEB (an umbrella group for European environmental groups) and the European Consumers Organisation BEUC (the umbrella group for consumer groups across Europe):

- 1) A full right to know, including what chemicals are present in products.
- 2) A deadline by which all chemicals on the market must have had their safety independently assessed. All uses of a chemical should be approved and should be demonstrated to be safe beyond reasonable doubt.
- 3) A phase out of persistent or bioaccumulative chemicals.
- 4) A requirement to substitute less safe chemicals with safer alternatives.
- 5) A commitment to stop all releases to the environment of hazardous substances by 2020.

The Charter has been welcomed by EU Environment Commissioner Margot Wallström, and was supported by the then Danish Environment Minister Svend Auken [64]. These five policies, taken

together, would create workable, precautionary, regulation of chemicals:

- A right to know would ensure that all decisions are transparent, and that consumers are allowed to make their own choices.
- A deadline for assessment of safety will get rid of the scandal of unassessed chemicals. We want safety assessment to use non-animal methods to the maximum extent possible; see [65].
- A phase out of persistent or bioaccumulative chemicals will stop the contamination of our bodies and environment, with chemicals having to rapidly break down into natural substances - with an exemption when these properties were an essential function in a specific application.
- Substitution will ensure that the safest possible chemicals - or techniques - are used.
- An end to releases of hazardous substances into the environment by 2020 will ensure that EU chemicals policy contributes towards the objectives of the OSPAR Convention, which aims to clean up marine pollution.

The intention of these proposals is to create a forward looking, sustainable chemical industry - not an industry fighting to retain outdated, unsafe chemicals.

5.4 Will the new system be able to cope with the biomedical revolution?

We now have a better idea of what sort of new EU regulatory system will emerge. There are some positive elements - for example, better safety data on all chemicals will increase the chance that problem chemicals will be dealt with earlier. However there are a number of issues under debate which will make a huge impact on whether the system will cope with scientific advances:

A fight over chemicals that contaminate

As is clear from the description above, there is still a considerable debate as to whether chemicals of 'very high concern' should include chemicals that accumulate in the body (very persistent, very bioaccumulative - vPvB and persistent, bioaccumulative and toxic - PBT). It is crucial for the future that these chemicals are phased out. Whether we currently understand them to be toxic or not, we are forcing ourselves to be exposed to them in the long term, even if we later find them to be toxic (using either classical methods or new ones), or we find that some individuals are much more susceptible to their effects.

Continuing secrecy about the chemicals present in products?

The current regulatory system allows the use of chemicals to be very secretive - it can even be difficult for major companies (eg Marks and Spencer's) to find out what chemicals are used in the

products they sell. This is enough of a problem now, but in a situation when new chemicals are being more rapidly identified as a problem the situation will be worse.

The chemical industry (in the Commission's technical working groups) has been pushing for less right to know than currently exists. Other parties are pushing for a right to know only for chemicals of very high concern, or which are proven hazardous. This is not enough to cope with new science.

As new problem chemicals are identified - which may not have been considered hazardous before - retailers, the public and downstream users will want to know if the products they buy contain these chemicals. They will want this information immediately on publication of the new research, not after years of debate on the precise hazardousness of individual chemicals. The current proposals will not provide this information. A general right to know is essential.

Secrecy for safety test data?

The chemical industry has been arguing that they should not have to disclose all the results of safety tests on their chemicals. It is crucial that this view is not allowed to prevail. For one thing, such secrecy is likely to lead to duplication of animal tests, which is unacceptable.

It is also important that the details of research are publicly available, as such information will be potentially useful in evaluating the significance of new research. For example, the full results of microarray experiments must be made available, as this data may be of use to other researchers who are working in the field, eg through confirming the involvement of a previously unknown gene in a toxic response.

No action on endocrine disruption?

The Commission's proposals - and those supported by the parliament - do not include the incorporation of endocrine disrupting chemicals in the authorisation process. Environment Council, and environmental NGOs, believe that they should be incorporated.

If endocrine disrupters are not part of authorisation, then the current lack of progress on regulating such chemicals will continue. This slow and ineffective process, based on proof of harm, will cause real problems as technologies such as microarrays (eg those developed by Syngenta) start identifying new endocrine disrupters and increase our knowledge about those endocrine disrupters that are well known (eg the can lining component bisphenol A).

No obligation to move to the safest chemicals?

The current EU proposals only go part of the way towards implementing the substitution principle, which should oblige companies to use the safest chemical available. Chemicals identified as 'very high concern' will be phased out through

authorisation, but many risky chemicals will not be caught through this process. Friends of the Earth believes it is essential that a general obligation is placed on industry to use the safest chemicals.

It is impossible to predict which chemicals will be found to be hazardous in the future – but it is likely that many chemicals currently known to be hazardous will be identified as having a higher hazard in the future – the substitution principle provides a method to encourage a move away from all hazardous chemicals.

Insufficient priority given to research, development and application of non-animal tests

The biomedical revolution offers a huge opportunity to develop non animal tests, through the development of much more powerful techniques using isolated cells, eg liver or cancer cells, and the use of more primitive model organisms eg yeasts or nematode worms.

The development and adoption of these new techniques will depend on real investment – both at European level and within Member States such as the UK. It is also essential that regulatory decisions in the new system can be made on the basis of such studies.

5.5 Are downstream industries acting on risky chemicals?

At the same time as the EU has been working on its new chemicals policy, Friends of the Earth in the UK has been surveying retailers and consumer product companies about their use of a short list of risky chemicals. The results of the latest phase of this study, published as a series of league tables [66], shows that whilst some retailers, such as IKEA and Marks and Spencer's, are taking action, most companies still appear to be ignoring the concerns around risky chemicals in their products.

In Friends of the Earth's view, it is in the interests of those using chemicals – including retailers – to take a precautionary approach to the chemicals they use in their products.

6. Conclusion

This update shows that in the fairly short period since the Crisis in Chemicals report was published there has been substantial scientific progress. At the same time, the review of regulations has made some progress – but current proposals have a number of significant flaws. Unless corrected, these flaws will mean that the new regulatory system will not protect consumers (or those who produce and use chemicals) from the health, environmental and financial consequences of new risky chemicals and new genetic susceptibilities.

It is clear that expression profiling research is advancing rapidly, and will start generating important results within the next couple of years. These results could, for example, include

identification of the likely toxicity of chemicals for which there is currently little safety data. In addition, the use of such techniques to better understand the complex systems of the body - the immune, nervous and endocrine systems – will identify new toxic effects.

Research on individual susceptibilities is moving more slowly, due to the complexities of multi-gene systems and epidemiology. However, it will clearly start to have an impact, and is already throwing up deficiencies in regulatory protection.

7. Recommendations

- It is essential that the EU's new chemicals policy is designed to cope with the increasing scientific knowledge that will come with the biomedical revolution. Specifically, it must include:
 - a full right to know what chemicals are present in products;
 - a phase out of chemicals that accumulate in the body, or have hormone disrupting properties;
 - investment in non-animal test methods, with precautionary regulatory action based on the results of these methods;
 - a general obligation on industry to use the safest available chemicals.
- All industrial sectors involved in making or selling chemicals and products containing chemicals should be taking a precautionary approach to the chemicals they use, and should be lobbying for a more protective regulatory system. Specifically:
 - the chemical industry should accept that a precautionary regulatory system is needed in order to protect itself from liability and loss of public and downstream user confidence;
 - downstream users should ensure they know what chemicals they are using, use only the safest chemicals, and accept that the era of the secretive 'snake oil' supply chain, where components are secret, must now end;
 - retailers should inform themselves as to what chemicals are in the products they sell, and should phase out those which are of concern;
 - the investment and insurance industries should ensure that companies they are involved with are taking a precautionary approach to the chemicals they're using.

Don't say we didn't warn you.

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