

# Crisis in Chemicals

The threat posed by the 'Biomedical Revolution' to the profits, liabilities, and regulation of industries making and using chemicals

FRIENDS *of the*  
**earth**  
*for the planet* for people

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## Executive summary

### 1. The Human Genome Project and related biomedical research – the 'biomedical revolution' – provides the biggest challenge ever to those who make, use and sell industrial chemicals.

**By 2010 Friends of the Earth predicts this research will have radically improved our understanding of what chemicals do to the human body. Without action now, there will be a crisis in the regulation and use of chemicals in the future.**

- The Human Genome Project and the research that is now flowing from it – the 'biomedical revolution' – is leading to a rapid acceleration in our understanding of how the body works.
- Increased understanding of how the body works makes it easier to detect the effects of chemicals – e.g. 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 get screened easily and cheaply, and discover if they are among the susceptible groups.
- New discoveries about the dangers of chemicals will spread ever more rapidly around the world, as research is made freely available on the Internet, and as Internet health and environment news services inform their subscribers. The public will demand to be protected from these dangers.

### 2. The industries involved in making and using chemicals are very vulnerable to the biomedical revolution.

- The **chemical industry** continues to manufacture and sell chemicals that accumulate in our bodies and the environment, without finding out how safe they are. Improved understanding of the workings of the body will improve the chances of liability cases succeeding. This industry will also be hit by actions from particularly susceptible people who live near polluting chemical factories and old waste dumps, and potentially by actions from affected members of their workforce.
- The **consumer products industry**, that sells chemicals to the public in its products, will be under increasing pressure from consumers to reveal what chemicals are in their products. With some components, such as perfumes or can linings, the consumer products industry may not even know the chemicals contained within them, due to the pervasive secrecy of their suppliers. Public concerns about chemicals in products could lead to product withdrawals. Susceptibilities and improved scientific knowledge could also lead to increased liability actions.
- If the public lose confidence in particular products, **retailers** may need to withdraw them from sale. In addition, retailers' own brands will be vulnerable in the same way as those from other consumer products companies. An inability to deal rapidly with developments in science, and requirements for protection, will result in damage to corporate reputations and brands.

- **Investors** will discover that companies that have not planned ahead and taken a precautionary approach to the use of chemicals will have their profits hit, and may even have their long term future destroyed by liabilities.
  - The **insurance industry** will be vulnerable to increasingly successful liability actions, and to losses from other forms of insurance held by affected companies, for example reputational insurance.
- 3. The biomedical revolution will increase public demand for rapid action from regulators to protect health and the environment. Currently, the regulation of the production and use of chemicals is totally incapable of dealing with such demands.**
- The current regulatory system is based on secrecy and ignorance. Regulators do not, in general, know the specific chemicals present in any product, and the vast majority of chemicals do not even have the most basic set of safety data. We are constantly exposed to poorly understood chemicals.
  - The current regulatory system for factory emissions allows continued discharge of hazardous chemicals. Even a senior UK Government official has accepted that the current system is relatively ineffective due to weak guidance notes and regulatory capture.
  - The inadequate regulatory system will make the regulator incapable of taking rapid action to cope with new science. People will not even be able to protect themselves, due to a lack of a comprehensive right to know what chemicals are present in products or released by industry. Without rapid and effective regulatory responses to new science, public confidence in regulators will collapse.

## Recommendations

- 1. A precautionary approach to the regulation of the use of chemicals is essential to ensure that the regulator is able to withstand the coming advances in biomedical science.**
- Most chemical regulation is at an EU level, and these regulations are currently under review. Friends of the Earth, supported by the European Environment Bureau, propose the following key policies to create an open, precautionary, regulatory system:
    - 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.**
  - These key policies will create a more open, responsive and precautionary regulatory system, more able to withstand advances in biomedical science. These proposals must be implemented in the current review – it usually takes a minimum of five years

for a new EU Directive to come into force, and biomedical science is advancing rapidly.

## **2. To protect itself, industry must take a precautionary approach to the use of chemicals.**

- The **chemical industry** must review the chemicals it produces, and abandon those which are persistent or bioaccumulative. It must ensure that it knows how hazardous the chemicals are, and what they are used for. It must move away from more hazardous chemicals in favour of low or minimal hazard chemicals.
- The **consumer product industry** must become far more aware of, and open about, what chemicals are used in products, and ensure that the safest possible chemicals or techniques are used.
- **Retailers** must quiz their suppliers to ensure that they are taking a precautionary approach with the use of chemicals in the products they sell.
- **Investors** need to be aware of the potential losses that could come from a company they are investing in because of concerns about a chemical it makes or uses. It is in the investors' best interest to pressurise companies to adopt a precautionary approach to the use of chemicals. They must not take a 'head in the sand' or conservative approach to this issue.
- **Insurers** must ensure that they assess all risks fully, taking into account possible future developments, particularly when covering product liability, withdrawals and company reputations.

**The next few years provide industry and the regulators with a window of opportunity to move to a precautionary approach.**

**The advance in science is relentless – the biomedical revolution won't stop. Now is the time to act to ensure that confidence in the regulator and industry is possible in the future.**

**Don't say we didn't warn you.**



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# 1 Introduction

**The chemical industry produces, uses and releases thousands of chemicals every year, and most have inadequate safety data. Even for chemicals known to be hazardous it is virtually impossible for someone to prove that they have been harmed by them. Over the next 10 years a revolution in our understanding of the human body will change this, with huge financial impacts on those industries which make or use chemicals.**

There are huge advances now underway in our understanding of the workings of the body, which will allow us to determine and measure the toxic effects of chemicals. In addition, we will soon know more about those individuals most susceptible to the effects of chemicals – and it will become politically untenable not to protect all the population.

The biomedical sciences are advancing rapidly, and by 2010 we will have sequenced the human genome, characterised much of the variability that exists between individuals, and learnt far more about the workings of complex systems of the body. Genetic screening will be becoming routine, a normal part of being prescribed many pharmaceuticals and a routine component of preventive health.

What has this got to do with risks from chemicals? Why should industry and regulators be concerned? This report examines two reasons why the biomedical revolution should concern those who make and use chemicals:

- 1) People vary in their responses to chemicals, and by 2010 we will know far more about this variation. Sensitive individuals will then demand to be protected.
- 2) As we understand more about how our bodies function, it will be easier to detect the effects chemicals have on us.

Industry will be faced by people, armed with scientific evidence, who want to avoid certain chemicals or who can show damage from exposure to chemicals. And industry will have to be prepared for loss of public confidence in its products, and increasingly successful liability claims.

Regulators will be challenged to protect the public, particularly once some individuals know that they are more sensitive to specific chemicals than the rest of the population.

This report outlines the current situation, describing the results of some important research that has already been undertaken. It also gives an indication of where future advances in this area will take us. A potential scenario is described in Box 1.

The report is structured as follows:

- Section 2 outlines the developing biomedical revolution or 'New Biology', as the huge resources being pumped into the Human Genome Project result in a revolution in our understanding of how the body works. Consequently, our understanding of the toxic effects of chemicals on the body will be vastly improved;
- Section 3 describes what is already known about genetic susceptibilities;
- Section 4 outlines the current problems with chemical regulation in the EU, and the implications of the biomedical

- revolution for confidence in the regulatory system;
- Section 5 outlines the implications of the biomedical revolution on liability and confidence in products, and how these issues will impact on the industries making, selling and using chemicals – and on those companies insuring them;
  - Section 6 outlines Friends of the Earth's proposals for more precautionary regulation and use of chemicals, and how such a policy will help industry and the regulators cope with the biomedical revolution.

### Box 1: A possible scenario

In 2010 a paper identifies that 0.1 % of the population are 100 times more sensitive to the toxic effects of chemical x. Chemical x is a common additive in plastics. The journal publishing this paper realises the importance of the research, and ensures maximum publicity on the day of publication. The public are alarmed, and some consult their doctors. By this time genetic screening equipment is becoming a routine part of a doctor's surgery and the doctor takes a swab of the patient's cheek for screening. The doctor has already downloaded the sequence of interest from the journal's Internet site, and the machine synthesises the necessary DNA or RNA for the test. The doctor also ensures that the sample is checked against a few thousand other genetic susceptibilities, to save time in future treatments.

Within minutes the doctor and patient will know if the patient is one of the 0.1%. If they are, the patient will want action – why is this chemical being used? What is it used in? How can I avoid it? The patient may also consult a lawyer to begin legal measures to reduce exposure and/or obtain compensation for existing exposure. All this could happen within hours of the paper entering the public domain – and it is likely to have been published in a free Internet archive, available globally to anyone who is interested.

Will the regulator and industry be able to answer the questions above? Or will secrecy and ignorance cause a loss of public confidence?

Maybe 0.1% of the population doesn't sound like much, but it's around 59,000 people in the UK or 300,000 in Europe – as a comparison, around 85,000 people in the UK have Multiple Sclerosis.

## 2 The biomedical revolution

**A revolution is now underway in the biomedical sciences – the sciences that study how the body works. For the first time, 'big science' techniques are being applied to the biomedical field, with huge amounts of money being pumped into the Human Genome Project and the research that will follow its completion. This knowledge will have immense impacts on our understanding of how the body works, and the toxic impacts of chemicals on it. Both the speed of scientific research, and the speed of its dissemination, will also accelerate.**

It is now feasible to look forward to a time when we have sequenced the human genome, and know a great deal about how the components of cells and the entire human body interact. In his book *Consilience: The Unity of Knowledge* [1], published in 1998, the biologist Edward O. Wilson discusses the expectations of scientists:

*"Let us suppose that early in the next century the hopes of the molecular and cellular biologists are fully realized. Suppose further that the researchers succeed in breaking a human cell down into all its component parts, track the processes, and accurately model the whole system from the molecules up. And suppose finally that the developmental biologists, whose focus is on tissues and organs, enjoy similar success. The stage will then be set for the final assault on the still more complex systems of mind and behaviour."*

### 2.1 Introduction to the biomedical revolution

The biomedical revolution, or 'New Biology' is a collection of scientific developments which flow from the sequencing of the human genome.

The human genome consists of 23 pairs of chromosomes, which are made up of DNA; Box 2 is a basic explanation of the genome and

genetics. The genome contains the bulk of the information needed to create the human body. One of the most important functions of the genome is to encode genes – templates describing the structure of proteins, which are one of the main building blocks of the body (see Figure 1). Some proteins are known as enzymes and carry out chemical reactions, for example in breaking down chemicals in the liver or in food digestion in the intestines. The human genome is estimated to encode 50,000 - 100,000 genes [2], though there may be more.

Not all genes are expressed (switched on) all the time – many are only active at certain times, such as during development [3]. There is therefore a complex set of mechanisms controlling gene expression, affecting the quantity of proteins made and when.

The biomedical revolution aims to understand how the human body works, which will require an understanding of:

- the human genome sequence;
- the structure and function of proteins encoded by the genome;
- when individual proteins and other cellular components are produced;
- how all cell components interact with each other, and how the body's cells interact and develop to form a human being.

As we learn more about all these processes we will be able to understand more about how our bodies work. For example we will be able to:

- discover who is most sensitive to the effects of toxic chemicals;
- find out how a chemical affects the immune system;
- prove links between disease and exposure to chemicals.

Research on all these aspects is underway, and is outlined below.

## 2.2 The Human Genome Project

At the core of the biomedical revolution is the Human Genome Project – a project to establish

### Box 2: A simple guide to genetics

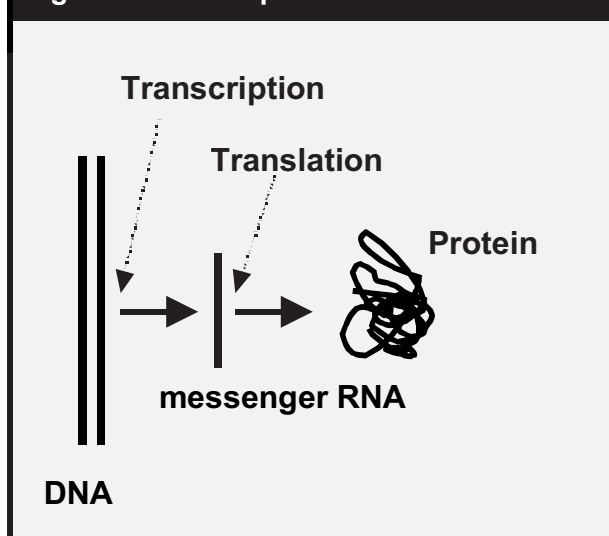
The instructions for making up an organism are contained in its **genome**, which is made up of tightly coiled threads of deoxyribonucleic acid (**DNA**). Each DNA molecule contains many **genes**, which contain the information required for constructing **proteins**.

Some proteins provide the structural components of cells and tissues, whilst others are **enzymes** which carry out essential biochemical reactions like digesting food or breaking down synthetic chemicals. Proteins are made up of a chain of **amino acids**, with the order of amino acids determined by the sequence of the DNA in the relevant gene.

The protein-coding instructions in the genes are **transcribed** from the DNA template into **messenger RNA (mRNA)** in the nucleus of a cell. This mRNA is then moved out of the nucleus, and is used as a template for the production of protein, where the mRNA sequence is **translated** into a protein sequence (see Figure 1). A variation (**mutation**) in a DNA sequence can result in a protein with a different behaviour than normal. In the lab, mRNA sequences are often translated back into DNA, producing complementary DNA (**cDNA**) – see Box 3 for some applications of cDNA. The individual elements of a DNA sequence are called **nucleotides**, and a short DNA sequence (often synthesised in a lab rather than naturally) is called an **oligonucleotide**.

This information is based on a primer produced by the US Department of Energy, available free on the web [4]. There is also a more advanced glossary in Box 5 on page 22.

Figure 1: DNA to protein



a full genetic sequence of a human genome. Sequencing the human genome is a multinational project, which started in the USA, with substantial participation by scientists in other countries, notably the Sanger Centre in the UK [5]. There is also a parallel, private sector, sequencing project run by Celera Genomics Corporation, which is using a combination of its own sequencing and the publicly available, publicly funded, Human Genome Project. There are concerns that Celera's efforts to make money from its genome sequencing will damage future research and development [6].

The full sequence was originally due to be completed in 2005 but technical advances have quickened the pace. A working draft, covering at least 90% of the genome, is due to be completed imminently, and a full sequence is expected to be completed by 2003 [7-9]. The first full chromosome sequence published, on 2<sup>nd</sup> December 1999, was that of chromosome 22 [10]. Chromosome 22 is one of the smallest human chromosomes, with about 1.6-1.8% of the total genomic DNA. In spite of this, the sequence consisted of 33.4 million bases, encoding for at least 545 genes. The first rough drafts completed were those of chromosomes 5, 16 and 19, published on 13<sup>th</sup> April 2000 by the Human Genome Project [9].

The Human Genome Project focuses on obtaining a single human DNA sequence. In reality, all of us have different sequences, although around 99% of the DNA sequence is the same in all humans. Following on from the

Human Genome Project, other research projects are underway to examine the diversity of humanity. An outline of three aspects of this research follows.

### 2.2.1 Mapping small variations in DNA

Single nucleotide polymorphisms (SNPs) are differences in single DNA base pairs, some of which will be relevant to the functioning of the body, for example affecting whether a particular enzyme is produced or not. The US Human Genome Project intends to map at least 100,000 SNPs [11]. In addition the SNP consortium, made up of the Wellcome Trust, 10 of the world's largest drug companies, five genome laboratories and IBM [12], has been created with the aim of characterising 300,000 SNPs and mapping half of them for use in epidemiological studies. The resulting database will be made freely available, and should be finished in less than two years [13].

### 2.2.2 The Human Genome Diversity Project

This project aims to characterise the genetic diversity of humans across the world, by examining the genomes of a wide variety of people. It is already known that many genetic susceptibilities are distributed differently among ethnic groups; this project should improve our knowledge of these variations. However, there are a range of ethical concerns surrounding this project, such as how those populations sampled should benefit, and what sort of controls there should be over use of the results (e.g. [14]). In addition, this project is having funding problems, as a result of these ethical concerns and competition with other human genome related projects [15].

### 2.2.3 Environmental Genome Project

The Environmental Genome Project is a US National Institutes of Environmental Health Sciences project which was launched in 1997, with the aim of documenting the occurrence of gene variations in 200 key genes which are relevant to susceptibility to exposure to chemical or physical agents. This project aims to identify who in the human population is more vulnerable to the effects of particular exposures [16]. It will take DNA samples from a large, ethnically diverse group of US citizens to study the different versions of the 200 genes. These 200 genes will be chosen by peer

review, and will contain representatives from 10 gene classes, including:

- xenobiotic metabolism and detoxification genes – genes that code for enzymes that break down foreign compounds in the body;
- hormone metabolic genes – genes encoding for the enzymes that create and destroy hormones;
- receptor genes – genes that encode for the receptors used to signal messages within the body, e.g. hormone receptors;
- DNA repair genes – that encode enzymes that repair damaged DNA;
- cell cycle genes – that encode enzymes and signalling molecules that control the way cells divide;
- cell death control genes – that encode enzymes and signalling molecules that control the death of cells, e.g. if they have been damaged and are in danger of turning malignant;
- genes that mediate immune and inflammatory responses;
- genes that mediate nutritional factors;
- genes that are involved in oxidative processes;
- genes for signal transduction systems that control expression of genes in the other classes. [16]

The Environmental Genome project will generate an immense amount of information about variations in susceptibility to chemical and other exposures.

## 2.3 Discovering the structure and function of the body's proteins

The proteome is "the complete set of proteins that is expressed, and modified following expression, by the entire genome in the lifetime of a cell" [17], or in other words, every protein that is ever produced in a cell. Proteomics is "the study of the proteome using technologies of large scale separation and identification" – analogous to genomics. Proteomics aims to develop rapid techniques to characterise the proteins in the cell, a step change from older techniques where months or years were spent examining a single protein. The science is already advancing rapidly:

*"Structure determinations that used to require large teams gutting out a 20 person-year effort now constitute a single chapter in a graduate student's doctoral thesis" [18].*

Proteomics is more challenging than genomics, as a whole range of new techniques will need to be developed, and existing techniques such as X-ray crystallography (to determine the structures of key proteins) and computer modelling will need to be scaled up.

An example of the resources now being devoted to computer modelling of protein folding is the announcement by IBM that they are starting a \$100 million research project with the aim of developing "Blue Gene", a supercomputer 500 times faster than the world's current fastest computers [19]. This computing power will be initially devoted to modelling protein folding, and IBM is expecting to produce a computer capable of one petaflop performance – one million billion (a quadrillion) operations per second – within five years, with around 50 scientists working on the project.

One outcome from proteomics and the Human Genome Project is that we should finally be able to locate and model the shape of every receptor in the body – receptors are involved in transmitting and responding to signals such as hormones or tastes. Researchers using the Human Genome Project's developing gene sequence have already identified a previously unknown family of bitter-taste receptors [20]. Modelling the structure of receptors will also enable modelling of what sort of chemicals bind to them, enabling screening of chemicals to determine which may activate – or block – the cascade of signals that are initiated by receptor binding. For example, this would make it very easy to establish which chemicals could disrupt the endocrine (hormonal) system – see Box 6, page 28 for more on endocrine disruption.

## 2.4 Finding out what proteins are produced when

Knowledge of what proteins are capable of being produced by an organism only takes us part of the way towards understanding the workings of cells – we need to know when and why different proteins are produced. The new technique of the DNA microarray is providing

a rapid and effective way of characterising what genes are being expressed in a cell at any one time.

A DNA microarray is a slide on which 10,000 or more DNA sequences have been spotted, using techniques similar to those used in semiconductor manufacture; see Box 3. The arrays can then be used to detect what mRNA (messenger RNA, which is copied from the genome's DNA sequence and then translated into a protein sequence) is present in a cell at any moment – a snapshot of which genes are turned on [21].

Much progress is being made to improve fabrication of the microarrays, with the aim of accurately spotting more DNA sequences on a single chip. Examples include the use of techniques similar to those used by inkjet printers, and the use of micro-mirror arrays (originally manufactured for projecting TV images). The latter has already managed to achieve 76,000 DNA sequences on one chip, increasing the number of tests that can be done per chip [23].

### Box 3: DNA chips – the basics

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 [22]:

#### (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.

In parallel with the advances in the technology for making these devices, scientists are starting to use them in real research. One of the first pieces of research published was an examination of the effects of ageing and caloric restriction (lack of food) on the skeletal muscle of mice [24]. This study looked at changes in expression of 6,347 genes – around 5-10% of the mouse genome – between young (five month old) and old (30 month old) mice, and found that 58 genes had a greater than two-fold increase in expression levels, whilst 55 showed a greater than two fold decrease. The researchers were able to identify the functions of these genes using previous research. To test the effects of caloric restriction on ageing, the researchers fed a group of mice on only 76% of the normal diet and found that at 30 months old these mice had far fewer signs of ageing than the ones on a normal diet. This provides more support for earlier research, which suggested that caloric restriction slows ageing. The pattern of changes in gene expression also showed similarities to that observed on caloric restriction in much simpler organisms – *Saccharomyces cerevisiae* (yeast) and *Caenorhabditis elegans* (a nematode worm).

## 2.5 Bringing it together – modelling the cell

Once the genome is sequenced, the proteome is understood and patterns of expression have been elucidated, then science will be ready to put all this information together into computer models of complete cells – and later whole organisms. The gathering of definitive answers is many years off, but as data starts to accumulate, attempts will be made to start modelling cells with the data available.

A Nobel prize winning cell biologist, Alfred Gilman, is now seeking funds for a multi-lab, multi-disciplinary project to model how molecules in cells interact with each other [25]. The intention of the project is to identify and characterise all the signalling pathways in two types of mouse cell – a B lymphocyte from the immune system and a myocyte from the heart. This project, the Alliance for Cellular Signalling, is a step towards the creation of a virtual cell – in which all cellular processes are modelled, allowing the impacts of perturbations, such as pharmaceuticals or

environmental chemicals, to be examined in a computer model of the cell.

There are other new scientific techniques in development that are also expected to provide more insight into the working of whole cells. One of these is the Integrated Optical Magnetic Resonance Microscope under development at the Pacific Northwest National Laboratory in Washington, USA. This microscope combines an optical microscope with nuclear magnetic resonance technology – a technology that is capable of identifying individual chemicals in a cell. This combination allows the microscope to observe the operation of a living cell, examining changes as the cell is exposed to different challenges – for example heating the cell or exposing it to toxins [26].

## 2.6 Applications of the biomedical revolution

It is clear that the advances in understanding brought about by the biomedical revolution will have extensive impacts on medicine; 89 medical journals have recently taken part in a global theme issue on the "Impact of new technologies in medicine" [27, 28]. These advances will create both solutions and problems, and it is important that the problems are examined fully to avoid undesirable consequences. Some examples of advances and concomitant problems follow.

### 2.6.1 Improved understanding of disease

It is the promise of improved understanding of disease that is the main driver for the current huge increase in funding for biomedical research. Improved understanding of disease will lead to improved treatments, and, more importantly, improved prevention. The pharmaceutical industry sees huge opportunities for the development of new treatments, and it is investing accordingly. New treatments will result from both discoveries about the differences between individual genetic predisposition to disease, and from the improved understanding of diseases themselves.

Expression profiling is already beginning to become a powerful tool in the understanding and diagnosis of disease. One of the first uses has been to examine differences between acute myeloid leukaemia and acute lymphoblastic

leukaemia. These two diseases look identical under the microscope, but have different treatments. Researchers used a DNA microarray of 6,800 genes, later focussing on 50 genes, to distinguish easily between the two cancers in 36 out of 38 samples. In addition, a patient with an atypical expression profile was found to have a completely different cancer [29]. Other research has managed to elucidate two forms of the commonest sub-type of non-Hodgkin's lymphoma using a DNA microarray with 17,856 genes [30]. Such techniques are likely to lead to far more understanding of different cancers, and will probably lead to several established cancers being divided into different diseases.

The Wellcome Trust has announced a £10 million 'Cancer Genome Project' at the Sanger Centre in Cambridge, with the aim of improving understanding of cancer mechanisms and assisting development of new treatments [31].

### 2.6.2 Genetic screening

Once it becomes clear that certain gene variants have medically important effects, then there will be pressure for screening to be available. This will happen initially in the pharmaceutical field, where the investigation of genetic variations in response to drugs is called pharmacogenomics (see Section 3.1 for more details). Genetic screening is very straightforward for the patient, as a simple brush of a swab on the inside of the cheek, or a blood sample, is all that is needed for reliable collection of DNA [32].

Rapid screening for tens of thousands of different variants is being made possible using DNA chip technology (as described in Section 2.4). Therefore, rather than testing for one susceptibility at a time, doctors will be able to screen some or all of the medically relevant susceptibilities. Chips with 60,000 DNA markers are being used in clinical drug trials by major pharmaceutical companies [33]. This information can then be used to devise individual doses for pharmaceuticals, or to select different drugs for different people.

The pharmaceutical company Glaxo Wellcome has already said that within the next 2-3 years it wants to market a new HIV treatment, Ziagen, with a DNA chip to test patient susceptibility to the medication [34]. As a

result of this new technology, Glaxo Wellcome is also lobbying for speeding up of the approval procedure for new medicines [35].

There are also proposals from the Wellcome Trust, in collaboration with the UK Medical Research Council, to set up a UK Population Biomedical Collection, which could eventually contain DNA samples from 500,000 people [36].

### 2.6.3 Gene therapy

Gene therapy – the modification of the genes of an individual – is a controversial aspect of the biomedical revolution. It will not be covered here as it is of limited relevance to the issues covered by this report.

### 2.6.4 Ethical and employment issues created by the biomedical revolution

There are many ethical issues involved in the Human Genome Project and the rest of the biomedical revolution. These issues have been discussed in some depth in other reports, for example the British Medical Association's 'Human Genetics: Choice and Responsibility' [37], the UK Human Genetics Advisory Committee's (HGAC) 'The Implications of Genetic Testing for Employment' [38] and in a special issue of the *Journal of Medical Ethics* [39]. Box 4 outlines some of the main conclusions of the HGAC report.

The main points that are particularly relevant here are:

- Friends of the Earth has not developed an ethical position, but would generally endorse the conclusions of the reports from the BMA report [37] and the HGAC, in particular the latter's conclusion that *"it would not be acceptable for genetic test results to be used to exclude people from employment or advancement on the grounds that they have a predisposition to future ill health"*[38];
- if screening is to occur, it should be used to allow individuals to make choices – for example which chemicals they wish to be exposed to;
- regulators and industry are obliged to protect the whole population, including more susceptible individuals;

- it is important to ensure that the degree of genetic determinism is not exaggerated. Care needs to be taken to ensure that public perception matches the science.

#### Box 4: Ethics of genetic testing

The UK Human Genetics Advisory committee's recommendations included [38]:

*"It would not be acceptable for genetic test results to be used to exclude people from employment or advancement on the grounds that they have a predisposition to future ill health...."*

*It would not be in anyone's best interests to ban the use of genetic test results for employment purposes completely.....*

*that... appropriate mechanisms are put in place to involve geneticists, employer and employee representatives and other stakeholders to monitor developments in the use of genetic testing and discuss the implications for employment...*

*an individual should not be required to take a genetic test for employment purposes...*

*an individual should not be required to disclose the results of a previous genetic test unless there is clear evidence that the information it provides is needed to assess either current ability to perform a job safely or susceptibility to harm from doing a certain job...*

*For certain jobs where issues of public safety arise, an employer should be able to refuse to employ a person who refuses to take a relevant genetic test..*

*any genetic test used for employment must be subject to assured levels of accuracy and reliability, reflecting best practice...any use of genetic testing should be evidence-based and consensual... professional advice should be available. Information about and resulting from the taking of any test should be treated in accordance with Data Protection principles...of fairness and lawfulness."*

Note that the HGAC is no longer operational; it has been replaced by the UK Human Genetics Commission, which started work in 2000 (<http://www.hgc.gov.uk>). The US Human Genome Project also undertakes ethical research; see <http://www.nhgri.nih.gov/ELSI/> for more information. The US Government has announced restrictions on genetic testing for employment similar to those suggested by HGAC [40].

## 2.7 The impact of the biomedical revolution on toxicology

Toxicology examines the effects of chemicals on the body, and the more that is understood about the workings of the body, the more can be found out about the toxic effects of chemicals. Some examples are:

### 2.7.1 Understanding individual susceptibilities

Some individuals are more susceptible than others to the toxic effects of chemicals, for example because their liver enzymes are not as good at breaking down these chemicals. The biomedical revolution, especially the Environmental Genome Project (Section 2.2.3), will identify more of these variations, whilst improved rapid screening techniques will make it much easier to identify susceptible individuals. Genetic susceptibility is examined in depth in Section 3, where examples are given of how science is beginning to identify the most sensitive.

### 2.7.2 Molecular epidemiology and biomarkers

One of the key problems in toxicology is identifying whether, and to what extent, an individual has been exposed to a chemical. Biomarkers, measurable changes in some element of the body, provide a method of monitoring exposure levels, and in some cases, early toxic effects. Biomarkers can be divided into four categories [41]:

- Internal dose – indicates how much of a chemical has entered into the body. In conventional epidemiology this would be calculated from levels in drinking water for example. Biomarkers of exposure allow this to be directly calculated, for example by measuring levels of a metabolite (breakdown product) in urine.
- Biologically effective dose – measuring how much of a chemical has reacted with critical biological molecules, such as chemicals that have bound to DNA, forming DNA-adducts.
- Early biological effects – markers of early cell responses to harm, for example, chromosomal damage.
- Markers of susceptibility – information on whether an individual is particularly

susceptible to a chemical, as discussed in other parts of this report.

The rapid progress in biomedical research, with associated advances in analytical techniques, is leading to an explosion in the number of biomarkers available, and in the understanding of their significance. As the presence of a biomarker proves exposure, they are very useful in providing evidence towards demonstrating that a particular chemical caused a particular effect, for example during legal action.

Biomarkers have been used to examine the effects of air pollution on the developing foetus [42]. By examining blood from the umbilical cord of newborn babies the researchers were able to measure the level of PAH-DNA adducts in the white blood cells. PAHs, or polycyclic aromatic hydrocarbons, are a group of chemicals, some of which are reproductive and developmental toxicants, mutagens and carcinogens. PAHs are widespread pollutants, produced by car exhaust, cigarette smoke and other burning processes. Air pollution was found to be significantly associated with the levels of PAH-DNA adducts in new born children, and those children with higher levels of PAH-DNA adducts had significantly lower birth weight, birth length and head circumference. Levels of PAH-DNA were higher in infants than mothers, showing that the foetus is more susceptible to genetic damage than the mother. This is the first study that has provided molecular evidence that PAH exposure of the foetus compromises foetal development – the promise of biomarkers is that many other methods will become available to examine the impacts of exposure to chemicals.

### 2.7.3 Expression profiling

Expression profiling was described above with reference to general medical applications of the biomedical revolution. It also has many uses in toxicology, especially in the field of toxicogenetics, the application of genetics to toxicology, and also toxicogenomics, the application of genomics to toxicology. As stated in a recent review: *"The fundamental assumption of toxicogenetics is that there are no toxicologically relevant outcomes in vitro or in vivo, with the possible exception of rapid necrosis [cell death], that do not require*

*differential gene expression"* [43]. Or, put another way, almost all toxic responses will change gene expression – which can be picked up by a DNA array.

The US National Institute of Environmental Health Sciences has already prepared an array of 2,100 human genes (the ToxChip) that have already been proven to respond to toxicological insults [44]. These arrays can be used to help compare and evaluate the toxic effects of different chemicals, to screen new chemicals and to find out more about the effects of mixtures.

### 2.7.4 Understanding the workings of cells and the body

As mentioned in Section 2.5, scientists are now investigating methods of modelling the workings of cells, and consequently the entire body. Understanding how the body works will make it much easier to measure the effects of chemicals on the body. For example, reliable measurement of the performance of the immune system will enable the identification of chemicals that damage it.

## 2.8 The information revolution

The speed of generation and distribution of new scientific information will increase hugely over the next few years. There are two main elements to this: an increase in the speed of science, and an acceleration of information distribution in the wider population.

### 2.8.1 The acceleration of science

The rate of scientific discovery and its communication is accelerating for two main reasons:

***(i) New technologies allowing more research to be done in less time***

As an article in November 1999's British Medical Journal stated [33]:

*"Genomic technologies are still evolving rapidly, at an exponential rate similar to the development of computer technology over the past 20 years. We are not certain where genomic technologies will be 10 years from now."*

***(ii) More rapid publication of scientific research***

The publication of new scientific research used to be a fairly leisurely affair, with sometimes

many months between submission of a research paper to a journal and its publication. Over recent years journals have accelerated their production processes to reduce this gap. There are now new pressures on the process – the creation of e-print archives on the internet, either attached to a journal or completely separate. The most developed of these projects is PubMed Central\*, sponsored by the US National Institutes of Health, which will be a huge, freely available, archive of research papers. The papers in this archive will be peer reviewed, but the publication process will be very rapid, and the research will be freely available to all [45]. The archive will also include free access to research papers from established journals, such as the British Medical Journal [46] – an editorial in the BMJ described PubMed Central as "the electronic database where all biomedical research may eventually be 'published'" [47]. There are also proposals for a similar European site, 'E-Biosci' [48]. The time lag between a new discovery in a lab and international access to the results will be radically shortened once these databases are fully in operation.

### 2.8.2 The Internet as a key information resource

In addition to the publication of research being accelerated, there will also be an acceleration, and a growing sophistication, in the way this information is communicated to the broad population, outside the scientific world. Such communication will be made possible by the growing strength of Internet-based sources of information.

A recent survey of 'cybermedicine' (medical information in cyberspace) estimated that there are currently over 100,000 health related web sites, and quotes a survey of web users in October 1998 in which 27% of female and 15% of male users said they accessed medical information at least weekly [49]. Over the next few years it is likely that there will be a move towards more focussed use of fewer, higher quality sites. Such sites could easily have a daily email newsletter, with the latest health news. New discoveries will be communicated faster, and with more detail, than ever before. No longer will health stories have to fight with

other news to get into newspapers, and then be given too little space for adequate background information. Those who wish to get detailed information will get it daily, and be able to use their trusted health sites to give them the background. These sites will be run by a range of organisations, including governments (e.g. NHS Direct in the UK<sup>†</sup>), academics, doctors, NGOs, organisations or companies specialising in the provision of health information, and the health industry (pharmaceutical companies and the purveyors of other health- and fitness-related products). Different health sites will clearly have different agendas.

### 2.9 The biomedical revolution – looking forward to 2010

The biomedical revolution will advance rapidly in the near future, and biology in 2010 will look very different from how it looks now. The human genome should be fully sequenced by 2003, and by 2010 genetic screening will probably be in routine use in medicine. The Environmental Genome Project will produce results, so it will be clear which are the key genetic susceptibilities relevant to toxicology. The advances in understanding of the complex systems of the body will be providing new methods of measuring harm from chemicals, and many new methods will be available for screening the toxicity of chemicals. Advances in our understanding of how our bodies work will have led to more chemicals being identified as hormone disrupters, immunotoxins and neurotoxins.

The next section examines genetic susceptibility in more depth, while the section after asks the question – can the regulatory system cope with the biomedical revolution?

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\* <http://www.pubmedcentral.nih.gov/>

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† <http://www.nhsdirect.nhs.uk/>



## 3 Genetic susceptibility in depth

**Research into genetic susceptibility is still in its early stages, even though it has been underway for many years. It is only just beginning to use the new techniques the Human Genome Project makes possible. What follows is only the beginning of the story of genetic susceptibility; over the next decade this field will advance very rapidly.**

One researcher in the field has stated

*"I believe that we have only seen the tip of the iceberg with respect to the influence of genetic predispositions on the development of childhood cancer" [50].*

This section examines what is already known about genetic susceptibility, and where the research is going. It focuses particularly on those enzymes involved in detoxifying chemicals, and also discusses variation in the endocrine and immune systems. There is a glossary for this section in Box 5 on page 22.

### 3.1 Pharmacogenetics

The influence of genetic characteristics on response to chemicals has been known for some time, though the initial focus was on pharmaceuticals, which led to the establishment of the field of **pharmacogenetics**. Pharmacogenetics came into being because of the observed variability in people's responses to certain pharmaceuticals. For example, Weber reports [51]:

*"Consider an episode that took place in the 1970s at St Mary's Medical School in London during a small trial with debrisoquine, a new therapeutic agent for treating high blood pressure. A number of healthy human volunteers were each given a small dose of the drug, and afterward one of the volunteers suddenly collapsed because of a drastic fall in his blood pressure. None of the other volunteers experienced anything out of the ordinary. After several days in*

*hospital the sensitive man had fully recovered, but the reaction in a healthy person was so startling that more tests were run to find the reason for it. The hyperresponsive individual was found to process the drug in a way that turned a normal dose into a massive overdose because he didn't make the normal enzyme required to hydroxylate the drug and eliminate it from his system. Further test led to the discovery of two medical students at St Mary's who also were unable to hydroxylate debrisoquine.....larger studies revealed that at least one in ten of the British population at large possessed the same trait. Later studies of family pedigrees showed that persons who are sensitive to debrisoquine carry a double dose of a defective gene for this trait."*

Fatal complications due to genetic susceptibility can arise when some individuals are given anaesthetics. After complications during anaesthesia for one 21 year old Australian, it was realised that of 38 relatives that had had general anaesthesia, 10 had died, emphasising the inheritance of genetic susceptibility [51].

Pharmacogenetics was first named by Vogel in 1959; in 1971 Brewer coined the term ecogenetics to describe the study of genetically determined differences in susceptibility to the action of physical, chemical and infectious agents in the environment [3]. This report uses the term 'genetic susceptibility' in preference to ecogenetics, as the term ecogenetics is seldom used.

The term pharmacogenomics is now being used to describe the use of information about many genes from the Human Genome Project,

### Box 5: Advanced glossary

Definitions of more basic terms are provided in Box 2 on page 12. Based on [22].

Allele	One of several forms of a gene at a specific locus.
Allozyme	An enzyme encoded for by an allele.
Conjugation	Attachment of a chemical group, often a glutathione or acetyl group, to make a chemical more soluble and easier to excrete.
DNA adduct	A chemical that has become bound to DNA
Genotype	The genetic makeup of an individual.
Heterozygous	Two different alleles at one locus.
Homozygous	Two identical alleles at one locus.
Locus	A unique chromosomal location defining the position of an individual gene or DNA sequence.
'Null'	Inactive or deleted gene.
Odds ratio	The ratio of the odds of disease for the group being examined when compared with a control group.
Polymorphism	The existence of two or more variants (e.g. alleles) at significant frequencies (often >1%) in a population.
Promoter	The area of DNA that RNA polymerase binds to in order to transcribe a gene from DNA to RNA.
SNP	Single nucleotide polymorphism. Any polymorphic variation at a single nucleotide site.
Trinucleotide repeat	A repeating pattern of 3 nucleotides, which, due to inaccuracies in DNA replication, can expand and cause effects.

as opposed to pharmacogenetics, which focussed on variations in one or two genes. The promise of pharmacogenomics includes the ability to avoid genetically determined severe drug toxicity, and the ability to individualise treatments, with different doses and types of drugs being used for different patients [33].

At a few US clinics, children with acute lymphoblastic leukaemia are tested for polymorphisms in the thiopurine S-methyltransferase enzyme prior to treatment, as the activity of this enzyme affects the child's sensitivity to thiopurines, drugs commonly used to treat leukaemia. Those children deficient in this enzyme are treated with lower drug doses. Similar tests are being developed for other pharmaceuticals [52], and it has been predicted that "*one day it may be considered unethical not to carry out such tests routinely to avoid exposing individuals to doses of drugs that could be harmful to them*" [53].

### 3.2 Basics of variability in toxic responses

Substances cause toxic effects because they interact with the body. A number of steps are usually associated with a toxic response, for example:

- 1) absorption into the body;
- 2) metabolism in the liver or another tissue, into a product which may be more or less toxic;
- 3) interaction with a part of the body, for example a receptor triggering a cascade of resulting actions;
- 4) excretion of the chemical, or its metabolite, from the body.

All of these processes can potentially vary between individuals.

Variation in response is not always due to variations in a single gene; in many (or most) cases multiple genes will be involved. This means that research will take time to come up with definitive answers; contradictory results will appear as single genes are studied individually. In some cases multiple relevant genes will lead to a 'Normal' distribution of susceptibility, rather than a simple on/off distribution – other distributions will also be

possible [3]. A recent editorial in Nature Biotechnology stated:

*"...in multifactorial diseases such as cancer, no single gene is responsible for the manifestation of the disease. It has become apparent that networks of genes – perhaps hundreds of genes and their products interacting with environmental stresses – are required for disease manifestation. Genetic predisposition to cancer, therefore, depends on all the other genes a person has, as well as on extrinsic factors and on that individual's unique history.*

*And so it will not, at the moment, be possible to come up with simple tests for cancer based on a single gene or genes that will have any real predictive value for large populations of people. We simply don't understand how all this works yet. And that's because we are still looking for ways to get beyond the one gene/one disease model of cancer" [54]*

Science is progressing rapidly, but there are many challenges ahead. The direction is clear, though – the understanding of how we work and how variations in our bodies cause us to respond differently to environmental challenges such as chemical exposures.

### 3.3 Detoxification systems

One of the most researched and understood areas of genetic susceptibility is the detoxification systems of the body. The body is able to break down or detoxify many chemicals using a small group of enzymes (biological catalysts). The bulk of detoxification occurs in the liver, but some occurs in other organs. Detoxification reactions are divided into two groups, phase 1 and phase 2 reactions: [55]

#### Phase 1

Phase 1 reactions generally convert chemicals into products that are more water soluble, through oxidation, reduction and hydrolysis reactions. There are two enzyme systems responsible for these biotransformations, the cytochrome P-450 family and the mixed-function amine oxidase. The cytochrome P-450 family is the most important, and is made up of a large number of related enzymes, which vary in the chemicals that they transform.

#### Phase 2

Phase 2 reactions generally involve conjugation or synthetic reactions – additions of new elements to the chemical, often after a phase 1 reaction has created an appropriate functional group. The addition of the new element makes the chemical more soluble and easier to excrete through the kidneys, liver or intestines. A range of phase 2 reactions are described below.

The interaction of these two enzyme systems creates a very complex system, in which some chemicals are actually made more toxic, and where imbalances in activity between the different systems can cause problems. Some examples of the influence of genetic susceptibility on these processes are described below.

#### 3.3.1 Cytochrome P450s

The cytochrome P450s are a large group of enzymes, with over 700 having been identified so far; not all of these are present in humans. They carry out phase 1 reactions, and in mammals they are divided into 4 families, CYP1, CYP2, CYP3 and CYP4. Within these families there is further subdivision into subfamilies, for example CYP1A and CYP1B, and the individual enzymes are given names such as CYP1A1 and CYP1A2 [56]. Not all cytochrome P450s lead to detoxification. In the case of compounds such as benzo[a]pyrene, CYP1A activates the chemical, making it more toxic.

This report will not describe in depth the roles of the different cytochrome P450s, but will briefly describe some of those for which a toxicologically significant genetic polymorphism has already been identified. Many studies show that metabolic variations are not just due to changes in CYP enzymes themselves, but also involve phase 2 metabolism, and other factors, for example the systems that control the production of the CYP enzymes. Such studies are described in 3.3.5 below.

Although genetic variation within the human CYP system is well known, the functional significance of many of the variations is still being established. It is clear that variations in CYP2D6, CYP2C19 and CYP2C9 are

significant in the metabolism of certain pharmaceuticals, as some polymorphisms result in very low or absent enzyme activity. However it seems that these CYP enzymes are not of great toxicological significance; polymorphisms in more toxicologically relevant CYP enzymes are less well understood and their roles are currently more controversial [57]. However, in a recent review of cytochrome P450s the authors state:

*"Genetically programmed differences in an individual's P450 expression profile will likely represent an important risk determinant of chemical toxicity" [56].*

It has been suggested that some deaths from ecstasy are due to genetic polymorphisms in the CYP2D6 enzyme, which is also involved in breakdown of many pharmaceutical agents. Around 5% of Caucasians have impaired metabolism of these compounds, which could lead to accumulation of the drug [58]. Pharmaceuticals known to be affected by this impairment include debrisoquine and metoprolol. There is also considerable ethnic variation in frequency of this polymorphism, e.g. 1% of Japanese people are affected, as against 15% of Nigerians [33].

### 3.3.2 Glutathione S transferase

The glutathione S-transferase (GST) family of enzymes carry out a phase 2 reaction, binding a glutathione to the chemical being detoxified (often after a phase 1 reaction), for example detoxifying oxygen radicals. They are divided into six classes, *Alpha*, *Delta*, *Mu*, *Pi*, *Theta* and *Zeta*. Important human enzymes include GSTT1 (*Theta* class), GSTP1-1 (*Pi* class) and GSTM1 (*Mu* class).

#### **GSTP1-1**

The polycyclic aromatic hydrocarbon (PAH) benzo[a]pyrene is a carcinogenic component of the gas produced by many burning processes, including cigarette smoke and car exhaust. It is activated in the liver by CYP enzymes and epoxide hydrolase, creating (+)-anti-benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide ((+)-*anti*-BPDE), which can bind DNA to form a DNA adduct, which is associated with cancer. However, this compound can be conjugated by GSTP1-1, leading to detoxification. GSTP1-1, the only functional *Pi* class enzyme found in humans, is

polymorphic, with amino acid variability at two locations, isoleucine or valine at amino acid 104 and alanine or valine at position 113. Hu et al. [59] have measured the effectiveness of the three different variants of GSTP1-1 that have been found in humans (I104, A113; V104, A113; V104, V113) in protecting cultured liver cells from adduct formation. Earlier experiments had already shown that enzymes with valine at both 104 and 113 were more active in conjugating (+)-*anti*-BPDE. Liver cells with V104 and V113 had significantly fewer adducts after an exposure to (+)-*anti*-BPDE than those with the other two variants, with cells with I104, A113 having the most adducts. However, adding to the complexity of the situation, earlier work has shown that although the VV enzyme is better than IA for detoxifying planar PAH-diol epoxides such as (+)-*anti*-BPDE, it is less active than IA for detoxifying nonplanar PAH-diol epoxides such as benzo[g]chrysene. Therefore, whether the VV variant is protective against cancer will depend on the specific mixture of PAHs that an individual is exposed to; the most frequent human variant is IA.

The isoleucine - valine variability in GSTP1-1 has also been found to be associated with a premalignant condition of the oesophagus [60]. The condition, Barrett's oesophagus, is a variation in the epithelium (skin) of the oesophagus, and people with this condition have 30-125 times the risk of developing oesophageal adenocarcinoma than the general population. This research found that individuals with Barrett's oesophagus or oesophageal adenocarcinoma were more likely to have the valine (V104) polymorphism. These workers also found that this polymorphism was associated with reduced enzyme activity, when measured with 1-chloro-2,4-dinitrobenzene. Note that this contrasts with the results for planar PAH-diols above, where the valine polymorphism is associated with greater enzyme activity. The complexity of these results demonstrates that we have some way to go before we fully understand these systems; this is not simple science.

#### **GSTM1**

The GSTM1 gene is one of the most extensively studied for the links between

polymorphisms and cancer risk [61]. An examination of 12 case-control studies of GSTM1 status and lung cancer risk found that GSTM1 deficiency is a moderate risk factor for development of lung cancer, accounting for almost 17% of lung cancer cases. One study examined the impact of this deficiency on lung cancer rates in women who had never smoked, but who had been exposed to tobacco smoke (passive smokers) [62]. This study found that those women with GSTM1 null had a significantly greater risk of lung cancer.

Some research has suggested that GSTM1 deficiency is more important when combined with other polymorphisms involving GSTP-1 or CYP1A1. A review published in 1998 concluded:

*"we probably have not reached the stage where results could be interpreted for preventative measures, e.g., to predict risk because of occupational exposure to mutagens and carcinogens, or to identify hypersusceptible workers and exclude them from working in jobs in which they may be exposed to high levels of carcinogens" [61]* (NB: See Section 2.6.4 for discussion of the use of genetic information in employment.)

### **GSTT1**

Dichloromethane is widely used in industrial applications, food processing and agriculture. One model of its mode of toxicity is that it is metabolised by GSTT1 to formaldehyde, which then reacts to form DNA-protein crosslinks or formaldehyde RNA adducts. A common GSTT1 polymorphism, 'null', is deletion of the gene; therefore those who are homozygous for this deletion will produce no GSTT1. In the case of exposure to dichloromethane, such individuals will actually be protected from the toxic effects, as they won't produce formaldehyde, if this model is correct. In reality it is possible that some formaldehyde production will result from the activity of other GST enzymes. This GSTT1 null polymorphism is unevenly distributed across ethnic groups, from 62% in Asians (including Chinese and Korean backgrounds), 21.8% in African-Americans, 19.7% in US Caucasians, and 9.7% in Mexican-Americans. GSTT1 null individuals will, however, be at higher risk from exposures to substances such as ethylene oxide or epoxy butene, for which

GSTT1 enzymes are important in detoxification [63].

### **Zeta class and more**

Board et al. [64] used one of the new genetic tools, an 'Expressed Sequence Tag' database, to attempt to locate previously undescribed phase 2 enzymes and polymorphisms. They were able to identify a new class of human glutathione transferases (*Zeta*) and new members of one of the already known classes (*Alpha*) and some new polymorphisms were identified. This research indicates the power of working up from a DNA sequence, rather than working down from which enzymes can be detected in cells.

### **3.3.3 Acetyl transferase**

Arylamine *N*-acetyltransferases NAT1 and NAT2 detoxify arylamines by acetylating them to give amides. However, in combination with CYP1A2 they may also activate arylamines, as CYP1A2 can produce reactive hydroxylamines, which NAT may then further activate by *O*-acetylation to acetoxyarylamines [65]. Both NAT1 and NAT2 have polymorphisms, though much currently available research has only measured one or the other. This current incompleteness of data, combined with the possible role NAT could have as an activator as well as a detoxifier, and problems linking changes in genotype with changes in phenotype means that traditional distinctions between individuals who are 'slow acetylators' or 'fast acetylators' may be rather over-simplified [66].

Low activity of NAT2 (or slow NAT2) has been found to be associated with urinary bladder cancer in smokers [65], and also with post menopausal breast cancer in Taiwan [67]. A slow NAT1 genotype (NAT1\*4/\*4) has been strongly associated with 4-aminobiphenyl DNA adducts [66]. A recent review of NAT1 and NAT2 polymorphisms concluded [68]:

*"Individual risks associated with NAT1 and/or NAT2 genotypes are small, but they increase when considered in conjunction with other susceptibility genes and/or aromatic and heterocyclic amine carcinogen exposures. Because of the relatively high frequency of some NAT1 and NAT2 genotypes, the attributable risk of cancer in the population may be high."*

### 3.3.4 Paraoxonase

Serum Paraoxonase (PON1) is an enzyme that detoxifies organophosphate compounds such as insecticides. The human PON1 gene has two common polymorphisms, arginine (Arg) or glutamine (Gln) at amino acid 192, and leucine (Leu) or methionine (Met) at amino acid 55. It appears to be only the former that affects the enzyme's catalytic properties, producing three genotypes QQ (Gln-Gln – formerly designated type A), QR (Arg-Gln) and RR (Arg-Arg – formerly designated type B). The two allozymes (forms), Q and R, hydrolyse organophosphates at different rates [69]. The Q allozyme hydrolyses (breaks down) sarin, soman (both nerve gases) and diazinon (a pesticide) more rapidly than R, but has a lower activity than R against paraoxon, a metabolite of parathion (a pesticide). Therefore the different allozymes of this enzyme can not be simply split into high and low activity, as this depends on the substrate.

A study of neurologically impaired Gulf War veterans found that they were more likely to have genotypes of either QR or RR rather than QQ. In addition, a low activity of the type Q enzyme was correlated with illness [69].

In contrast, a study of farmers chronically exposed to organophosphates such as azinphos-methyl, chlorpyrifos and malathion (all pesticides) found that farmers with the QQ phenotype (identified through tests of enzyme activity) showed more inhibition in acetylcholinesterase activity, an enzyme in the nervous system which is the target of organophosphates [70].

Other researchers have emphasised the importance of measuring how much PON1 is present in the body, as well as which form of the enzyme is expressed. The more PON1 present, the more protection against the toxic effects of chlorpyrifos. Individuals with the same genotype can have up to a 15-fold variation in expression of this enzyme; the reason for this variation is not yet known [71]; there could, for example, be polymorphisms in the promoter of the enzyme.

#### ***Paraoxonase and other detoxification enzymes in farmers***

An examination of chromosome damage and detoxification enzyme polymorphisms in Costa Rican farmers found that those with

'unfavourable' polymorphisms were more susceptible to genotoxic effects than those with more favourable alleles [72]. The study looked at a range of detoxification systems, including paraoxonase (unfavourable: QQ genotype), cytochrome P450 2E1 (unfavourable: base substitution in transcriptional region causing over-expression of the gene, which activates small organic chemicals), and the glutathione *S*-transferases *mu* and *theta* (unfavourable: deletion).

### 3.3.5 Studies of both phase 1 and phase 2 metabolism and disease

Some studies are now examining if there are links between specific illnesses and a range of polymorphisms of phase one and phase two metabolism. Some examples follow.

#### ***Childhood Acute Lymphoblastic Leukaemia***

Acute lymphoblastic leukaemia (ALL) is the commonest childhood cancer, but it is not known what causes susceptibility to the disease. As part of attempts to locate susceptibilities, polymorphisms of detoxification genes were studied in 177 ALL patients and 304 controls in Quebec [73]. The study examined CYP1A1, CYP2D6, GSTM1 and GSTT1 genes. The GSTM1 null (no activity) and CYP1A1\*2A (elevated activity) were each associated with increased risk of ALL (odds ratio 1.8). Individuals with both of these polymorphisms had an even higher risk (odds ratio 3). CYP1A1 is involved in activating chemicals such as PAHs, so increased activity could have negative effects, particularly if the GSTM1 null genotype leads to reduced conjugation of the activated PAHs. One additional result from the study was that females with the CYP1A1\*4 allele were less likely to have ALL, suggesting that this allele may provide some sort of protection. The biological significance of this mutation is unknown, though it is also possible that an adjacent gene, linked to this one, may be causing the effects. More research will be needed to establish the role of genetic susceptibility in ALL, and then to examine what chemical exposures must be avoided to protect those who are sensitive.

#### ***Renal Cell Carcinoma***

Renal (Kidney) cell carcinoma (RCC) is increasing by about 2-3% per year in

industrialised countries. Various dietary and environmental factors have been linked with RCC, including smoking, a high protein diet and working in the coke oven industry or jobs exposed to petroleum products or dry cleaning solution. Longuemaux et al. [74] have examined polymorphisms in xenobiotic (foreign compound) metabolism in 173 cases and 211 controls. The polymorphisms examined were in CYP1A1, CYP2D6, NQO1 (NAD[P]H: quinone oxidoreductase), GSTM1, GSTT1, GSTP1 and NAT2. The research found that individuals with at least one copy of 'variant' (more inducible, i.e. more 'switched on') CYP1A1 had a 2.1 fold increased risk of RCC. There was also a higher risk for this genotype combined with other genotypes, including NAT2 'slow acetylators', and for some other genotypes. The authors conclude:

*"These positive findings suggest that interindividual variation in the metabolic pathways involved in the functionalization and detoxification of specific xenobiotics is an important susceptibility factor for RCC in Caucasians."*

#### **Parkinson's disease**

As an example of the complexities of trying to relate illnesses with genetic susceptibility, the role of CYP2D6 polymorphisms in susceptibility to Parkinson's disease is currently under some dispute. A study by Hubble et al. [75] that CYP2D6 29B+, a poor debrisoquine metaboliser allele, was more common in patients with Parkinson's disease with dementia (the more severe form) than in Parkinson's disease without dementia. However, research by Sabbagh et al. [76] found no difference in distribution of CYP2D6 mutations and alleles between Parkinson's disease patients, control subjects and affected and unaffected members of Parkinson's disease families. More research is clearly required before the role of genetic susceptibility in Parkinson's disease is clearly elucidated.

#### **Autism**

Autism is now believed to have a neurological basis; it is not, however, clear what causes the neurological damage that characterises the illness. However, one theory is that there may be an influence from toxic xenobiotic chemicals. Edelson and Cantor [77] examined the burden of xenobiotics and liver

detoxification processes in 20 autistic individuals. All 20 cases had liver detoxification profiles outside of normal, and 16 of the 18 cases which had blood analysis done contained xenobiotics at higher than acceptable adult maximum values. Chemicals found at high levels included toluene, ethylbenzene, triethylbenzenes and trichloroethylene. Earlier research found that 90% of autistic patients studied had a deficiency in the liver detoxification enzyme phenosulfotransferase.

The authors propose that autism results from a genetic defect in liver detoxification enzymes, which means that normal exposures to household chemicals are not detoxified, and damage to the brain occurs – probably whilst the child is still in the foetus, and the blood-brain barrier is incomplete. If this theory is correct, then control of exposures to household chemicals during pregnancy could have an impact in preventing (or ameliorating) autism, particularly in borderline cases, where the metabolic enzymes may be only partially dysfunctional.

#### **Tobacco related cancers**

In addition to the studies on smoking and cancer and GSTM1 mentioned above, other studies have found effects from several detoxification enzymes. One of the strongest links found was a 123-fold greater risk of developing oral leukoplakia, a precancerous lesion, associated with chewing tobacco or betel quid, among those individuals with both GSTM1 and GSTT1 null genotypes [78]. The same researchers have also studied the levels of bulky DNA adducts such as (+)-anti-benzo-(a)pyrene-diol-epoxide-DNA (BDPE-DNA) adducts, formed as a result of exposure to polycyclic aromatic hydrocarbons (PAH) such as benzo (a) pyrene in tobacco smoke, air pollution or occupational exposures. Smokers with a CYP1A1 variant and GSTM1 null had the highest adduct levels, and were the most susceptible to lung cancer. They conclude [78]:

*"..the examination of BDPE-DNA adducts resulting from the GSTM1 and CYP1A1 polymorphisms and their interaction with other susceptibility markers like mutagen sensitivity and impaired DNA repair capacity will help to identify high-risk subjects among smokers and subjects occupationally and/or*

*environmentally exposed to PAH. There is growing evidence that predisposing polymorphic genes, involved in carcinogen metabolism and repair, increase cancer risk in certain subjects, even when exposed to only low levels of carcinogens."*

### 3.3.6 Detoxification systems combined with other polymorphisms

#### **Aromatic hydrocarbon receptor and CYP1A1**

Daly et al. [57] examined activity of CYP1A1 in the lymphocytes (white blood cells) of 32 Caucasian individuals, and attempted to correlate variations in activity with various polymorphisms. They found no correlation with CYP1A1 genotypes, but did find a correlation with a change in the gene encoding the aromatic hydrocarbon receptor (*AhR*). This receptor, which is activated by chemicals such as dioxins and PCBs, is the transcriptional regulator for CYP1A1 – its activity controls

#### **Box 6: The problem of endocrine disrupting chemicals**

The endocrine system is responsible for many elements of the development and behaviour of the body, for example the sex hormones oestrogen and testosterone are responsible for the development and maintenance of reproductive organs. The endocrine system depends on small changes in the concentrations of the signalling molecules, and is therefore vulnerable to any chemicals which are capable of imitating, or affecting the concentrations of, these signals.

In recent years it has become clear that a range of industrial chemicals are capable of imitating or blocking the effects of hormones, for example bisphenol a, a constituent of some food can linings, and alkylphenols, used in some detergents. The US Environmental Protection Agency is undertaking a massive screening programme to establish which chemicals are endocrine disrupters [79]. As this screening programme starts generating results, it is expected that new chemicals will be identified as endocrine disrupters.

One major issue is the level at which endocrine disrupters are active; research on bisphenol a has found effects at very low levels [80]. Advances in biomedical science will have a huge impact on the understanding of how the endocrine system works, and how chemicals are able to affect it.

how much CYP1A1 is made. The polymorphism, *AhR* G<sub>1721</sub>A, is found in 12% of Caucasians, and led to a more than two fold increase in the level of the enzyme activity that is due to CYP1A1. More research will be needed to evaluate the significance of this result.

### 3.4 Endocrine system

Over recent years many concerns have been raised over the discovery that some industrial chemicals are able to imitate hormones, and so disrupt the endocrine system of humans and animals; see Box 6 for more details.

The endocrine system is complex, with a large number of potential processes which could be impacted by genetic variation, including:

- metabolism of endocrine-active substances, including natural hormones & synthetic endocrine disrupters;
- specificity of endocrine receptors for binding endocrine-active substances;
- level of transcription of response genes;
- activity of response genes.

Research in this area is at a fairly early stage; some examples follow.

#### **3.4.1 Variation in susceptibility to oestrogens in rats and mice**

There is currently much research looking at the effects of chemicals which can affect the hormonal system. Many of these experiments have been done with a well-known strain of laboratory mice, CD-1. However, recent research has shown that there are substantial variations in the susceptibilities of different mouse strains to natural oestrogens, with strain CD-1 being the most oestrogen-resistant strain tested [81]. Maturation of spermatids was eliminated by a low dose of 17  $\beta$ -oestradiol in two other strains (C57BL/6J and C17/J1s), whilst maturation in CD-1 mice was virtually unaffected by a dose of oestradiol 16 times higher. The authors suggest that the reason for the oestrogen-resistance of CD-1 mice is that they have been bred for large litter sizes. If these mice (or similar) are used to test potential endocrine disrupters then the results may underestimate the effects these chemicals may have on other organisms such as humans.

Another study has examined variations in response of rat varieties to the xenoestrogen bisphenol a, used as a component of many food can linings [82]. This investigation found that bisphenol a (BPA) was able to increase DNA synthesis in the vaginal epithelium of one rat strain, Fisher 344, but not in another, Sprague-Dawley. They were also able to confirm that there were no differences between the strains as regards their metabolism of BPA, its binding to the oestrogen receptor or even in the resulting immediate early gene transcription. The strains also responded identically to the natural oestrogen oestradiol. The research concluded that the difference between the strains' response to BPA must be due to a currently unknown delayed or intermediate effect.

The human implications of this research are not yet known, though it has been clear for some years that there is variation in response to the contraceptive pill [81].

Research examining the bioaccumulation of BPA in mice has also found inter-individual variability. Multiple doses of BPA given to pregnant mice led to substantial inter-individual variations in serum bisphenol a levels. Around 10% of the animals accumulated approximately ten-fold higher levels of bisphenol a than their treatment group averages. The cause of this variation has not yet been established [83].

### 3.4.2 Breast cancer susceptibility and the androgen receptor

Much breast cancer susceptibility research has focussed on *BRCA* genes, particularly *BRCA1*, as a mutation in this gene is associated with an increased risk of breast cancer. Recent research has examined how this increased risk is modified by variations in the androgen receptor ('male' hormone receptor), which is known to affect breast tumour growth and progression [84].

The expression of *BRCA1* is regulated by steroid hormone pathways, and it is known that the gene for the androgen receptor has a highly polymorphic CAG trinucleotide repeat (*AR-CAG*). The longer the *AR-CAG*, the lower the transcriptional activation by the androgen receptor, with patients with 40 or more repeats having androgen insensitivity – they do not respond to androgens. The research examined

women who had *BRCA1* mutations, 165 of whom had breast cancer and 139 had not got breast cancer.

The researchers found that women with at least one *AR* allele with more than 27 *AR-CAG* repeats were at significantly increased risk of breast cancer, and all 11 women with more than 28 repeats in at least one allele had breast cancer. Those women with more than 29 repeats in at least one allele were given a diagnosis of breast cancer 6.3 years earlier than those with <28 repeats on both alleles. This research indicates the potential importance of inherited variations in the endocrine system in susceptibility to cancer. Although this research focuses on the role of natural androgens, differences in susceptibility to chemicals which can imitate or block the action of androgens may also be important.

### 3.4.3 Prostate cancer susceptibility

Prostate cancer is known to be androgen-related, and also shows substantial ethnic variation, with incidence in African Americans > Whites > Japanese and Chinese. Research is underway to examine the contribution of genetic susceptibility to the incidence of this cancer, examining the genes involved in androgen biosynthesis, androgen inactivation, androgen transport and genes transactivated through the androgen receptor [85].

There are two steroid 5 $\alpha$ -reductase enzymes, both of which convert testosterone to dihydroxytestosterone, which is more active at the androgen receptor than testosterone. The type II enzyme is active in the prostate, and is encoded by the *SRDA2* gene. An analysis of mutations of this gene found that a valine (V) to leucine (L) substitution at codon 89 was common in healthy men, but displayed considerable ethnic variation, with a VV genotype in 59% of African Americans, 52% Whites and 30% of Chinese and Japanese, whilst LL genotype was found in 19% of Chinese and Japanese, 10% of Whites and 3% of African Americans. There was a strong correlation between this genotype and levels of androstanediol glucuronide, which correlates to prostatic 5 $\alpha$ -reductase activity, with lower levels with the LL genotype.

Variations in the androgen receptor have also been examined, including the finding that

shorter AR-CAG repeats are associated with prostate cancer, due to increased activity of the androgen receptor (in contrast to the case in breast cancer above). Other preliminary results have located single nucleotide polymorphisms that are associated with increased risk of prostate cancer; research is continuing to locate genetic variations which affect susceptibility to this cancer.

#### **3.4.4 Ethnic variation in DDT levels in humans**

It has been known for some time that there are ethnic variations in the amount of the pesticide DDT found in serum. The DDT metabolite p, p'-DDE has antagonistic (blocking) activity at the androgen (male hormone) receptor [86]. In American research in the 1970s it was found that after adjustment for age and socio-economic status, black males were found to have higher serum total DDT (DDT + DDE) than white males. Research in the 1980s suggested that the general decline in adipose levels of DDT following restriction on its use was significantly slower in black individuals than in white. The reasons for these differences are not yet understood [87].

### **3.5 The immune system**

The Editorial in the first edition (September 1999) of the new journal 'Genes and Immunity' states:

*"It is now clear that almost every aspect of the immune system contains genetically defined variation.....It is equally clear that this variation is likely to impact on all theatres of immunological activity" [88].*

The immune system is relevant to a range of responses to toxic substances, particularly lung responses such as asthma, but it is also implicated in conditions such as multiple chemical sensitivity. The immune system itself is extremely complex, and elucidating its genetic variability will be a challenging task. Some progress is already being made; some examples follow.

#### **3.5.1 Sensitivity to asthma**

Research is beginning to find links between variations in DNA sequence and susceptibility to allergic asthma. One recent study has examined the gene that encodes for the asthma-associated cytokine (signalling molecule) IL-13. Higher levels of IL-13 are

associated with the symptoms of asthma. The researchers found a polymorphism in the promoter of the IL-13 gene which led to increased production of IL-13 due to reduced effectiveness of factors which would normally inhibit production of IL-13. This polymorphism was found to be more common in asthmatics than in the general population, so may be a susceptibility factor for the development of asthma [89].

Polymorphisms of enzymes involved in breaking down or conjugating xenobiotics in the lung would also be expected to have an impact on lung sensitivity to exposure to chemicals.

#### **3.5.2 Sensitivity to ozone**

It is known that there is considerable variability in the response of people to exposure to ozone air pollution. Research on mice is beginning to establish a potential genetic basis for some of this variability. Researchers examining ozone-sensitive strains of mice have identified some suspect areas of their genome, in particular, the gene encoding the cytokine tumour necrosis factor- $\alpha$ , which is involved in promoting inflammation in the immune system [90]. Neutralising this factor with an antibody significantly protected against ozone injury in susceptible mice.

If these findings are repeated in humans, then it will become possible to identify genetically the section of the population who are most susceptible to ozone exposure [91], and there will be pressure to further reduce ozone air pollution, to ensure that those who are sensitive are protected.

#### **3.5.3 Autoimmune diseases**

Research is beginning to establish that polymorphisms of several genes are associated with susceptibility to, or protection from, autoimmune diseases such as rheumatoid arthritis, type I diabetes and multiple sclerosis. This research is at an early stage, and so far little attention has been given to examining the role of environmental exposures. One example of an autoimmune disease associated with exposure to chemicals is chronic beryllium disease. This disease is associated with exposure to beryllium, and some progress has been made in identifying markers of susceptibility [92].

## 3.6 Other systems

### 3.6.1 DNA repair systems

It is important for cells to ensure that their DNA remains in good condition. Each cell has a range of DNA repair systems for repairing small changes to the DNA, and also has mechanisms to ensure that any problems during cell division are resolved. The latter are described as cell cycle checkpoints, and consist of a complex group of messengers which are able to cause cell division to pause if there are problems. This pause may lead to the apoptosis, or programmed cell death, of the cell concerned, or it may just allow more time for whatever is wrong to be repaired. DNA repair mechanisms are crucial to the body, as DNA is constantly under attack, from UV light, radiation and DNA-binding chemicals – and DNA damage can lead to cancer.

One common chemical which leads to DNA-binding is benzo [*a*] pyrene, a polycyclic aromatic hydrocarbon which is present in car exhaust and cigarette smoke, and which is metabolised in the body into reactive products which can bind DNA. DNA repair ability does vary between individuals, and some diseases are already known to be associated with deficiencies in the function of cell cycle checkpoints [93]. Further research is needed to fully elucidate the links between deficiencies in repair systems and increased susceptibility to the effects of DNA-damaging chemical and physical agents.

### 3.6.2 Lead toxicity

Lead inhibits aminolevulinic acid dehydratase (ALAD), an enzyme that is involved in heme synthesis, and decreased ALAD activity results in an increase in free  $\delta$ -aminolevulinic acid in the blood, which has been proposed to be one of the mechanisms of lead's neurotoxicity. There are two common alleles of ALAD, ALAD1 and ALAD2, leading to three phenotypes, ALAD 1-1, ALAD 1-2 and ALAD 2-2. In a study of male lead smelter workers in British Columbia, it was found that those with ALAD 1-2 phenotype (ALAD2 phenotype) had higher blood lead concentrations than those with ALAD 1-1 phenotype (none had ALAD 2-2 phenotype). However, it was not clear whether this higher blood lead was having any adverse health impacts, though it was clear that the ALAD

polymorphism was affecting the toxicokinetics (adsorption, distribution and excretion) of lead. The study concluded:

*"The role of the ALAD genetic polymorphism in conferring genetic susceptibility to the adverse health outcomes associated with lead exposure has yet to be clearly defined" [94].*

Other polymorphisms, including that of the vitamin D receptor, are believed to be associated with variations in susceptibility to lead toxicity [95].

## 3.7 The future

We already know quite a lot about what systems of the body are going to be most important in determining susceptibility to chemicals, but we are only at the start of characterising this susceptibility. The next 5 to 10 years will see rapid advances in understanding individual susceptibilities.

This research will show us who is sensitive to what chemicals. The demands of these sensitive individuals to be protected will be a major challenge to both regulators and industry, a challenge which is discussed in the next two sections.



## 4 Can the regulatory system cope?

**There is a system for regulating the use of chemicals, but it is deeply flawed, and there is little public confidence in it. The biomedical revolution is transforming our knowledge about the effects of chemicals and individual susceptibilities to them. Will the, already flawed, regulatory system be able to cope?**

Different exposures to chemicals are regulated in different ways, including:

- regulations on (non pesticide) chemicals used in products, usually described as 'industrial chemicals' – discussed in detail below;
- regulations on use and residue levels of pesticides;
- regulations on emissions from factories and waste disposal operations;
- regulations on contamination of land;
- regulations on air quality;
- health and safety regulations;
- regulations on liability, access to information and access to justice.

The main regulatory system discussed in this section is for the marketing and use of industrial chemicals. However, all regulatory systems will be impacted by the advances in biomedical science, as they all depend on assessing the dangers posed by chemicals. Box 7 briefly describes some of the deficiencies in these other regulatory systems.

The European Commission is currently reviewing the regulation of marketing and use of industrial chemicals, largely because of the widely acknowledged deficiencies in the current system, described in more detail below.

### 4.1 Public confidence in regulation

Public confidence in regulators is already low – and their confidence in industry is lower. The most recent opinion poll examining attitudes of the European public on the environment, in

spring 1999 (16,144 people in total, see [97]), found that only around 10% of the public trust the Government as a source of environmental information. Environmental protection organisations are the most trusted, with around

#### Box 7: Other regulatory systems involving chemicals

**Regulation of pesticides and biocides** does include a requirement for basic safety data on the chemicals before they can be placed on the market. However, the regulations do not properly consider the effects of mixtures, or individual susceptibilities.

**Regulation of factory emissions** allows companies to get away with producing a substantial quantity of pollution – see Box 8 for two of the worst examples in Britain. Even a UK Government official has accepted that the current system is relatively ineffective due to weak guidance notes and regulatory capture [96]. This regulatory system also neglects the effects of mixtures and individual susceptibilities.

**Contaminated land** regulation fails to address mixtures and susceptibilities, and relies heavily on threshold levels that have little scientific backing.

**Air quality** regulation does not address mixtures and susceptibilities – which could be particularly important with ozone (see Section 3.5.2). Air quality regulations also tend to focus on a very small group of chemicals, ignoring many pollutants.

**Health and safety** regulations also largely ignore individual susceptibility and mixtures.

51% of the public trusting them as a source of information. Industry was the least trusted of all the organisations, with only around 2% trusting their information.

This poll also demonstrated the level of public concern about chemicals. When asked which factors could affect their health in the future, chemicals were of most concern, followed by air quality, food quality, water quality, waste, climate change, noise and finally building materials. The public (around 47%) also strongly supports 'making regulations stricter, with heavy fines', as against relying on industry initiatives or scientific progress, which was only supported by around 8%.

Public confidence has been affected by many issues, including non-chemical issues such as BSE and genetically modified food. In the chemicals field the public has observed the continuous drip, drip effect of chemicals being banned after many years of industry lobbying claiming them to be safe. The challenge now is for regulators to regain public confidence.

## 4.2 Current regulation of chemicals use

The bulk of the regulation of chemicals use is controlled at an EU level, with legislation starting in 1967:

*"...when it was recognised that provisions relating to the classification, packaging and labelling of substances on the market, in particular dangerous industrial chemicals, should be harmonised throughout the Community in order to eliminate the barriers to trade that national provisions in the Member States could represent." [98]*

The regulatory system can be divided into four types of regulation, with grey areas between them: [98].

### 4.2.1 Classification and labelling

The earliest EU chemicals legislation, Council Directive 67/548/EEC, created a system for standardisation of classification, packaging and labelling of dangerous substances; this has since been amended a number of times. Directive 88/379/EEC covers similar areas for 'preparations' rather than substances. Some classifications, for example 'carcinogenic', 'mutagenic' or 'toxic to reproduction' may result in bans on marketing and use to the

general public under yet another Directive, 76/769, after an assessment including economic and social implications.

### 4.2.2 Reactive regulation – restrictions on marketing and use

Directive 76/769/EEC (known as the 'limitations directive') provides for harmonisation of restrictions on chemicals. This directive tends to be used as a reactive tool, after a Member State has raised concerns about a specific chemical. Restrictions agreed under this directive usually only limit substances for specific uses, rather than banning them completely.

### 4.2.3 Gatekeeping proactive regulation

Unlike reactive regulation, where products are on the market until they can be shown to be dangerous, gatekeeping regulation doesn't allow a substance onto the market until it has

#### Box 8: Polluting factories

In spite of all their rhetoric about caring for the environment, many chemical companies still discharge substantial amounts of pollution. In England and Wales, two of the worst companies are Associated Octel and ICI at Runcorn [99]:

**Associated Octel** in Ellesmere Port reported that they had released 84 tonnes of lead and 7,013 tonnes of miscellaneous volatile organic compounds, including 4,001 tonnes of chloroethane, into the atmosphere in 1998. Associated Octel manufactures 80% of the world's output of tetraethyl lead – the lead in leaded petrol – in this plant. The main users of leaded petrol are now in the developing world, where Octel lobbies governments to ensure that lead is not banned – whilst the World Bank has said that there is 'no excuse for continuing to allow leaded fuels in any city' [100].

**ICI's Runcorn** plant released over a thousand tonnes of both trichloroethylene and 1,2-dichloroethane and nearly 476 tonnes of dichloromethane into the atmosphere in 1998. ICI is also having problems with pollution from a waste dump near this plant, see Box 14 on page 45.

Friends of the Earth's Factory Watch site provides information about factory releases in England and Wales:

<http://www.foe.co.uk/factorywatch/>

gone through some sort of assessment. In the case of industrial chemicals, all those chemicals which have been introduced to the market since 19<sup>th</sup> September 1981 have had to go through the 'new chemicals' notification procedure. This incorporates some level of pre-market testing and assessment, though this is still inadequate as, for example, it does not incorporate tests of endocrine disruption (see Box 6 on page 28). This process was introduced as an amendment to 67/548 (above). All new substances are listed on the European List of Notified Chemical Substances (ELINCS).

#### 4.2.4 Backlog proactive regulation

Gatekeeping regulations can deal with introductions of new substances that occur after the regulations come into force. However, these do not apply to products already on the market – the unassessed backlog. In the case of industrial chemicals, these are regulated through regulation 793/93, the 'Existing Substances' regulation. All chemicals on the European market between 1<sup>st</sup> January 1971 and September 1981 have been listed in the European Inventory of Existing Commercial Chemical Substances (EINECS); any substance not on this list must go through the New Substances procedure above. The EINECS database has 100,106 entries, though in reality there are fewer chemicals actually on the market. The latest data from the European Chemicals Bureau shows that there are 2,593 high production volume chemicals (HPVs), produced or imported in volumes exceeding 1,000 tonnes per year, and approximately 8,500 low production volume chemicals, produced or imported in volumes between 10 and 1,000 tonnes per year [101]. No one knows how many very low production volume chemicals, produced or imported in volumes lower than 10 tonnes per year, are on the market.

The aim of Existing Substances regulation is to assess the environment and health risks of Existing Substances, through setting priority lists for assessment. Chemicals on priority lists are then assigned to Member States to produce a risk assessment, and if necessary, risk management proposals. These risk management proposals may then feed into the restrictions on marketing and use regulations. No time limits have been set for existing

substances to be assessed, and at the time of writing this process had not been completed for a single chemical – one of the deficiencies of the process, but not by any means the only one.

### 4.3 Deficiencies in current regulation of chemicals use

There are many deficiencies in the current regulatory system. Some of these were outlined in a European Commission report in November 1998 [98], but there are also others. Some relevant deficiencies are described below; others are described in reports by the European Environment Agency [102] and the European Environment Bureau [103].

#### 4.3.1 Safety data

As mentioned in Section 4.2.4 above, no time limits have been set for the assessment of existing substances. This has meant that the chemical industry has been under very little pressure to find out how dangerous its chemicals are – even though people are still exposed to them. A US NGO, the Environmental Defense Fund, first highlighted in 1997 the lack of basic hazard data about even high volume chemicals. The latest data from the European Chemicals Bureau, responsible for collating information on chemicals in the EU, has shown that the same problem exists in Europe [104]:

- only 14% of the EU high production volume (HPV) chemicals – those produced and imported at over 1,000 tonnes/year – have a full 'base set' (the minimum set) of hazard data;
- 65% of HPV chemicals have incomplete

#### Box 9: A scandalous lack of safety data

Only **14%** of high volume chemicals (>1,000 tonnes/year in the EU) have the **minimum set** of basic safety data.

**21%** of high volume chemicals have **no safety data**.

**Only 30%** of high volume chemicals have even minimal information on whether they **accumulate in our bodies**.

There is even less known about lower volume chemicals.

(See text for details.)

data – for example only 30% of HPV chemicals have even minimal information on bioaccumulation;

- 21% of HPV chemicals have no data;
- there is even less information available about those chemicals produced or imported in volumes of less than 1,000 tonnes/year.

There are many other deficiencies in the safety data available on chemicals. For example, chemicals are not currently tested for hormone disrupting effects, even though tests are now becoming available. At a recent meeting of those who regulate the use of chemicals in the EU, one regulator accepted that in reality the majority of chemical substances are not covered by current legislation, as there is insufficient data available to even decide which are priorities [105].

The Scientific Committees employed by the European Commission have been surprised by the lack of safety data available on chemicals, for example when discussing some alternatives to phthalate plasticisers:

*"The view was expressed that, in general, it is somewhat surprising that these high volume chemicals are not supported by a more definite and better database. Considering the various requirements for testing such as those applying to pesticides and food additives, it would look as if these are compounds that have passed through the safety net" [106]*

#### 4.3.2 Persistence and bioaccumulation

Many chemicals in use do not break down well in the environment – they are persistent. Many also accumulate in humans and wildlife – they bioaccumulate. Chemicals that bioaccumulate in fat are liable to contaminate breast milk; a recent review by WWF found that over 350 chemicals have been found in human breast milk [107]. Some of these chemicals are already banned in most countries, such as polychlorinated biphenyls or DDT, whilst others are still in widespread use, for example artificial musk perfumes and brominated flame retardants. [Note that all medical advice is that breast milk is the still the best option for a baby.]

Chemicals that persist in the environment have also caused problems. One example is the

chlorofluorocarbons (CFCs), used as refrigerants and promoted because of their stability – until it was found that they were destroying the ozone layer.

A major problem with chemicals that persist or bioaccumulate is that if they are later found to be toxic there is no way to withdraw them from the environment or remove them from our bodies. In contrast, when chemicals that break down rapidly are banned, they will almost immediately disappear from the environment and our bodies.

#### 4.3.3 Right to know

The existing regulatory system does not provide consumers, regulators or industry with a right to know what chemicals are present in most products. In addition, companies are only obliged to disclose some of their safety testing – for example, in vitro tests are usually exempt.

Even Government agencies are not able to get full information from industry. For example, the UK Ministry of Agriculture, Fisheries and Food commissioned research to examine how much of a chemical called BADGE was leaching from can linings into products (particularly fish). The researchers were able to find some information about what can lining systems were in use, but weren't able to find out everything:

*"A surprising result was that BADGE was also found in some of the cans lacquered with a polyester coating. However, after discussion with industry it was found that low molecular weight epoxy resins can also be added to polyester coatings, although their function here is not known" [108]*

The 'existing substances' assessment process is also disrupted by the lack of information available about what chemicals are used for. For example:

*"As only the uses of a substance known to the Rapporteur and those involved in reviewing the report are assessed, it could happen that a potential risk is not assessed simply because a particular use of a substance is not common in the EU or not known to the 'Rapporteur'. A good example of this is acrylamide. The risk assessment under the Regulation was virtually completed when an accident occurred in Sweden, where*

*acrylamide was used or produced in situ, in circumstances which have still to be clarified, during the construction of a railway tunnel. Without this accident, the evaluation would not have focussed on the use of the substance as a grouting agent in tunnels, because this use was not known in Europe". [98]*

#### 4.3.4 Reality of mixtures

In the real world we are always exposed to mixtures of chemicals. Our bodies are contaminated with a wide range of chemicals; we are exposed to air pollutants, and chemicals in our homes and at work. In spite of this the assessment of the safety of chemicals – risk assessment – almost invariably assumes that we are only exposed to one chemical at a time. This is in spite of research that shows many chemicals, such as oestrogen mimics, act in an additive way – each chemical adds to the effects of the previous one [109]. Toxicology has also long recognised that some toxins can have greater than additive effects when an organism is exposed to them – this is called synergism [110].

#### 4.3.5 Susceptible groups

The current regulatory system does not adequately consider the most susceptible members of society. Genetic susceptibilities are virtually ignored, but these are not the only relevant susceptibilities. The developing foetus, infants and children can all be particularly susceptible and there are also increasing concerns about the elderly [111].

##### ***Developing foetus, infants and children***

Children are different from adults in a number of ways which can lead to increased susceptibility to chemicals, including:

- many parts of their bodies are developing, so are more susceptible to alterations, for example their brains and reproductive organs;
- they have a less developed ability to break down chemicals;
- they eat, drink and breathe more for their weight than adults, so they take in more (relatively speaking) contaminants;
- they tend to be breathing air closer to the ground, which may contain more dust than that higher up;

- they are more likely to put things in their mouths and eat things they shouldn't [112].

The developing foetus is also extremely sensitive to toxic chemicals, as the development of the body depends on complex interactions of signalling chemicals, and disruption of these signals can permanently damage the body's development.

In the USA the special vulnerability of infants and children is beginning to be recognised and investigated as a result of an Executive Order from the White House [113]. Though EU regulators can consider children, there has not been the same focus on ensuring we know about children's patterns of exposure and particular susceptibilities.

A solid indication that regulation is failing to protect the unborn child comes from disturbing research on foetal malformations in women occupationally exposed to solvents. This study followed 250 pregnant women in Toronto, Canada, half of whom were occupationally exposed to solvents, e.g. painters, printers and chemists [114]. Significantly more foetal malformations, 13, occurred among foetuses of solvent exposed women, when compared with non-exposed – only one. This research indicates that even in a country like Canada, health and safety controls on exposure to chemicals are not sufficient to protect the developing foetus.

##### ***Genetic susceptibility***

As this report makes clear, we are still at an early stage in our knowledge of genetic susceptibilities. There are the beginnings of a discussion of how variations in susceptibility will affect the setting of safety levels, for example a UK Government/Research Councils Initiative on Risk Assessment and Toxicology [115]. The main conclusions of this study were that more research is needed:

*"Further work should be undertaken on interindividual variations in toxicokinetic and toxicodynamic parameters, in particular on the inherent variability within the human population due to genetic factors affecting the metabolism of chemicals. In particular, in vitro screens should be developed further to determine the metabolic pathways for chemicals and their regulation in humans, in*

*order to estimate the size of population subgroups that have a genetic deficiency in metabolism"*

The current regulatory system usually uses a 100-fold safety factor for setting an acceptable daily intake (ADI) for a chemical when using toxicity data from an animal test. This 100-fold safety factor is made up of a 10-fold safety factor for extrapolation from other species to humans, and another 10-fold safety factor to account for human variability (note that there is no safety factor for considering the effects of mixtures). One of the reports in the UK Government study states that:

*"The analyses indicate that the composite 10-fold factor [for human variability]...is adequate except for subgroups which show major differences in kinetics or dynamics compared with the population mean" [116]*

It is these subgroups that this report is concerned with – and these subgroups could consist of hundreds of thousands of people.

For example, if one polymorphism was present in 10% of the population and led to a 10-fold increase in a risk, and another polymorphism was present in 10% of the population and led to another 10-fold increase in the same risk, then 0.1 % of the population would have both polymorphisms, and have a 100-fold increase in the risk. Note that this example assumes that the two polymorphisms are not genetically linked, and that their effects are additive.

This 0.1% would be around 59,000 people in the UK, or 300,000 people in the EU. This number of people can not be ignored by regulators – and if the individuals concerned know who they are, through screening, then they could be a considerable political force. In comparison, around 85,000 people in the UK have Multiple Sclerosis.

#### **4.4 Impact of the biomedical revolution on the regulator**

As new research is published, the regulator will have to cope with new demands for information and protection. These demands will have to be met – or the regulatory system will be in crisis.

##### **4.4.1 Demand for rapid action**

Research outlining a new chemical hazard or susceptibility will be disseminated very

rapidly. The regulator will then be expected to act quickly to ensure that this new information is incorporated into the regulation of the relevant chemicals. However, the current regulatory systems are not able to act rapidly, for example:

- the current 'existing chemicals' process, in operation since 1993, has been unable to complete a full risk assessment and risk management process for even one of the initial 110 chemicals that were to be examined [117];
- even well established hazards take a very long time to result in restrictions, e.g. lead in petrol has only just been banned in the EU, on the 1<sup>st</sup> of January 2000. Even now, Italy, Spain and Portugal have a derogation allowing them to sell leaded petrol for two more years [118].

A new regulatory system, based on the precautionary principle, is needed so that it is able to reduce future problems and react more rapidly when problems arise. Such a system is outlined in Section 6. Without such improvements, the system will not be capable of competent regulation or of restoring public confidence in the regulator.

##### **4.4.2 Demand for information**

When new concerns arise the public and media will require information. What products is this chemical in? How dangerous is it? Why is it there? Can it be substituted? Are you going to ban it?

With the current system, the regulator will only have a vague idea of what products the chemical is in. For most chemicals, they will not know how dangerous they are, because of lack of safety data. They will not know much about why it is used, or what might be able to substitute for it. The regulator simply will not have the information necessary for a rapid ban with the current regulatory system.

##### **4.4.3 Demand for protection**

Those who, through screening, discover they are more susceptible to certain chemicals, will demand that their health is protected. So rather than a theoretical small percentage of the population, this will be a real group of people. It will not be acceptable to state, for example, that 99% of the population are protected. Everyone will demand to be protected and it

will be the responsibility of the regulator to do this – and fast.

The lack of information and regulatory control systems will mean that this demand for protection cannot be met with the current regulatory system.

#### 4.4.4 Legal duties of the regulator

Governments and their regulators have duties to protect people – some of these are codified in specific regulations, whilst others are more overarching and result from legislation such as the European Convention on Human Rights. Emerging new science will challenge these legal responsibilities:

- **Responsibilities in specific regulations.** When permission is given to allow a discharge, or a chemical in a product, the regulator often has a responsibility to protect health. Someone who is more susceptible to the chemical concerned may challenge this decision in the courts, claiming that they have not been adequately protected by the actions of the regulator. In the UK this process is known as Judicial Review.
- **Overarching Government responsibilities.** The European Convention on Human Rights includes a right for respect for home and for private and family life. This article has been successfully used in a challenge to the European Court of Human Rights covering pollution from a waste treatment works in Spain (*Lopez Ostra v Spain*, 1994) [123]. It could potentially be used in the future by an individual challenging whether the Government was adequately protecting them from pollution or a chemical in a product.

#### 4.4.5 How can the regulator deal with these demands?

If little or nothing is done to restructure the regulatory system, it will not be able to cope with the biomedical revolution. There will be further loss of confidence in the ability of Government and regulators to protect the public, with associated damage to EU industries.

Industry – particularly retailers and consumer products companies – will also expect the regulator to provide them with information and

#### Box 10: The cost of regulatory failure – BSE and CJD

BSE (Bovine Spongiform Encephalopathy, or Mad Cow Disease) became widespread among cattle in the UK in the mid-1980s. It had either been spread to cattle through feed made from sheep infected with Scrapie, or BSE may have already been present in the cattle population and the use of cattle in cattle feed caused its increased transmission. Both BSE and Scrapie are spread by a prion, a deformed protein, and they both lead to a gradual destruction of the brain of victims.

Once the existence of the BSE outbreak was revealed, there was concern that it might spread to humans. There was already a similar human disease, CJD (Creutzfeldt-Jakob Disease), a fatal neurodegenerative disorder.

For 10 years the UK government position was:

*"There is currently no scientific evidence that BSE can be transmitted to humans or that eating beef causes CJD in humans. That issue is not in question"* (John Major, The Prime Minister, December 1995)

Less than four months later, after 10 cases of a new form of CJD in young people, the then Secretary of State for Health, Stephen Dorrell, said that:

*"The most likely explanation is that these cases [of CJD] are linked to exposure to BSE before the offal ban in 1989"*

This statement led to the virtual collapse of the British beef industry, a total export ban and a cost running into billions of pounds.

No-one knows whether the number of CJD cases will be in the tens, hundreds or thousands – as at 30<sup>th</sup> March 2000 there were 67 definite and probable cases of the new variant of CJD – now called vCJD – in the UK, and one case in France [119]. The public inquiry into the BSE crisis is itself costing £15 million [120].

Even after the Government acceptance of the probable link (which has since been confirmed [121, 122]), the Beef Industry at first continued to produce posters stating 'There is no proof of a link between BSE and CJD', whilst not mentioning that the link was 'likely'. Statements of this sort are very dangerous for industry, since if (or when) new evidence appears, they have to back down, and the industry loses even more public confidence.

guidance. Will the regulator be able to provide this?

A previous example of regulatory failure is given in Box 10, where poor regulation resulted in the spread of BSE in cattle, and the consequent spread of vCJD to humans. The BSE case also highlights an example of regulators and industry trying to ignore a problem, only to be overtaken when the reality of scientific cause and effect becomes established.

Friends of the Earth believes that it is possible to redesign the regulatory system so it is better able to survive the biomedical revolution. Section 6 (page 47) outlines the policies we believe are needed, and also discusses when these changes in regulation must be implemented.

## 5 Future problems for industry, shareholders and insurers

**The advances in science described in this report will have major impacts on the private sector, from increased demands for information, through forced product withdrawals, to increasingly successful liability actions.**

Those making and selling chemicals have so far, in general, managed to avoid pressure on, and liabilities for, their products. This is largely due to the difficulty of demonstrating that a substance has harmed someone – or even that a substance is harmful. The biomedical revolution changes this – and this will have a radical effect on those companies that are not prepared for it.

The pressures likely to result are described below, followed by an examination of how they will impact on different industry sectors.

### 5.1 Increased demands for openness and information

Industry is very secretive about the chemicals present in its products (as described in Section 4.3.3), except when it is obliged by regulation to be more open. New information about the safety of chemicals and individual susceptibilities will lead to increasing demands for information about the chemicals present in products. The consumer will not accept claims of 'commercial confidentiality'.

In addition, the public will not be impressed by the use of chemicals for which there is no, or insufficient, safety data. The demand will be for chemicals that have been shown to be safe beyond reasonable doubt.

The secrecy and ignorance of the current system is not sustainable; attempts to continue it will accelerate the public's desire to avoid chemicals as much as they can.

### 5.2 A need to rapidly change chemicals used in products

In the past, it has been possible for industry to rely on the slow, 'drip, drip' of new scientific information on hazards of a chemical, giving industry time to gradually shift to a new formulation. As science accelerates, this approach will no longer be tenable. As new research is publicised, those most susceptible people will demand protection immediately, as will the general population if new general health hazards are identified.

All industries will need to be aware of exactly what chemicals they are using in their products. A commitment to risk reduction will also be necessary, as outlined in Section 6.1, to reduce the chances of being faced with problems.

### 5.3 More successful legal claims

It has traditionally been very difficult to pursue legal claims against industry for harm from chemicals. This is mainly because liability has been difficult to prove, because science has not been able to show a definite link between an exposure and an effect.

A legal action for liability generally has to answer three questions [124]:

- can the substance concerned cause the health effect;
- was the plaintiff exposed to the substance, and if so, to how much were they exposed;

- did the substance concerned cause the health impact.

The level of evidence to demonstrate liability varies in different jurisdictions. In English Law it is usually the balance of probabilities. There are also variations in whether the defendant must be shown to be 'at fault' (e.g. knowing about the toxic effects of a substance) or not.

In some legal cases it is not necessary to show that harm has been done. For example under the law of Statutory Nuisance in England and Wales, which is relevant for pollution from industrial operations, anything complained of must be either 'prejudicial to health or a nuisance'. No harm needs to be shown, only that the activity is injurious or likely to cause injury [125].

The EU Product Safety Directive 85/374/EEC amended by 1999/34/EC establishes a no fault system (with some opportunity for a 'state of the art' defence), in which the injured person must establish [126]:

- the actual damage;
- the defect in the product;
- the causal relationship between damage and effect.

The causal relationship has in the past been very difficult to establish, for example due to:

- the often long delay between exposures and health effects;
- the difficulty in measuring many health effects, for example immune system damage;
- the reality that many illnesses have a range of causes, so it is difficult to show that a chemical exposure was the cause – one exception is asbestosis, which has consequently led to successful liability actions, see Box 11.

The biomedical revolution will have several impacts on this process, as described in Section 2.7:

- increased ability to identify and measure damaging effects of chemicals, through improved understanding of disease, the workings of the body and techniques such as expression profiling;
- improved ability to measure exposure, through biomarkers such as DNA adducts,

and improvements in chemical analytical techniques;

- the ability to prove special susceptibilities, through genetic screening. It has been established, at least in England and Wales, that companies must in general protect all individuals, even if they have unusual susceptibilities – the so-called 'egg-shell skull' rule [132].

As research advances, liability cases will start to become more successful. Susceptible and affected individuals will also group together – a process that the Internet will make increasingly easy. These groups will be better able to mount liability cases, and will also work to ensure maximum publicity for their case. Industry will also be vulnerable to liability cases from their own employees, if they can show their working environment has

#### Box 11: Liability and asbestos

Industrial use of asbestos started around 100 years ago, became more widespread following World War Two, peaked in the mid-1970s and is now declining rapidly as the different forms of asbestos have been banned. Exposure to asbestos has been unequivocally shown to cause mesothelioma and lung cancer, providing the vital link required to show liability [127].

The British company Turner and Newall were once the world's largest manufacturer of asbestos; in the 10 years up to 1995 they paid out around £350 million to settle claims from people with asbestos related illnesses [128]. A US study predicted that there would be 200,000 asbestos-related deaths in the US in the 25 years following 1992, costing asbestos manufacturers and their insurers \$50 billion [129]. In Western Europe deaths from mesothelioma are predicted to increase from 5,000 per year in 1998 to about 9,000 per year in 2018, with a total of around 250,000 deaths over the next 35 years [130].

The insurance market that has been worst hit by asbestos claims is Lloyd's of London, which reinsured many of those hit by asbestos claims. Lloyd's almost went bankrupt, whilst many of its investors, the 'names', did go bankrupt; some are now suing Lloyd's, alleging fraud. Lloyd's has already lost tens of billions of pounds on asbestos claims – but it's still not known what the final loss will be [131].

damaged them.

The cost to industry of successful liability cases is immense, e.g. asbestos, Box 11.

#### 5.4 Public confidence in products

It will become increasingly challenging for industry to retain public confidence in its products. Product withdrawals will become more common, while companies unable to answer questions about what chemicals are present in their products will suffer severe impacts on their public images. The scenario given in Box 1 on page 10 is a possible future example.

A past example of a company damaged by a loss of confidence in its product is Perrier – see Box 12.

#### Box 12: A loss of confidence – Perrier

In February 1990 Perrier found out, from US regulators, that its bottled water was contaminated with between 12.3 and 19.9 parts per billion (ppb) benzene (a carcinogen), above the US Food and Drug Administration limit of 5 ppb. These findings were given worldwide publicity. Days of confusion over the cause of the problem followed, with Perrier making several incorrect statements. The product was eventually withdrawn from the shelves across the world – 70 million bottles in the US alone. The problem was eventually isolated to a carbon filter at the French plant, which had not been replaced when it should have been [133]. Perrier's sales depended on its 'pure' and healthy image – and that image was severely damaged.

In 1991 it was reported that Perrier's share of the US take home mineral water market, their biggest overseas market, had gone down from 13% to 9%, while in the UK it had gone from 49% to 30% [133]. In the meantime, other brands benefited from Perrier's problems – in the UK one brand's sales shot up six times [134].

The Chairman and founder of Perrier resigned after the incident, and the company put aside \$78 million from their 1989 accounts and \$71 from their 1990 accounts in order to cover the costs of the benzene incident [135]. Overall production of Perrier declined from 1.25 billion bottles in 1989 to 700 million in 1993; it was taken over by Nestlé in 1992, with a substantial number of jobs lost [136].

Section 2.8 describes the increasing acceleration in the dissemination of new scientific research., and postulates the future development of health media on the Internet. The combination of these two changes will lead to a more rapidly informed and concerned global public. This will mean that rather than problems emerging initially in one country, as has tended to be the case in the past, they will emerge in many countries. This global concern can be financially damaging, as the example of Monsanto and genetically modified foods has shown – see Box 13.

The concerned public will demand rapid and comprehensive information – and action. The information must be honest – one of the best ways to destroy public confidence is to be misleading, and/or make statements that will not stand the test of time, as occurred during the BSE crisis (see Box 10).

#### 5.5 Regulatory tightening

Following on from the lack of public confidence in the regulatory system, the pressures to tighten up regulation are substantial. Section 6 describes Friends of the Earth's proposals for the current EU review of chemicals policy. However, in addition to this review other regulatory changes are also on the agenda, including:

- **The European Commission's Communication on the Precautionary Principle** [137]. This emphasises the importance of this principle to the EU regulatory process, and will probably lead to its greater application in chemicals regulation, particularly when dealing with uncertainty:

*"The absence of scientific proof of the existence of a cause-effect relationship, a quantifiable dose/response relationship or a quantitative evaluation of the probability of the emergence of adverse effects following exposure should not be used to justify inaction. Even if scientific advice is supported only by a minority fraction of the scientific community, due account should be of their views, providing the credibility and reputation of this fraction are recognised."*

*"Decision-makers need to be aware of the degree of uncertainty attached to the results of the evaluation of the available scientific*

*information. Judging what is an "acceptable" level of risk for society is an eminently political responsibility."*

- **The European Commission's Green Paper on Producer Liability** [138]. This paper is part of a consultation process on the application of the current directives on product liability. It discusses possible changes, including reducing the burden of proof on the victim, reducing exemptions from 'No Fault' liability and the introduction of a system for group actions.
- **The European Commission's White Paper on Environmental Liability** [140]. This proposes strict liability for damage to individuals and to important wildlife sites caused by dangerous and potentially dangerous activities regulated by EU environment related law, e.g. factory discharges or landfill sites.

## 5.6 Financial impacts on the chemical industry

The chemical industry is ultimately responsible for the production of chemicals, so it is particularly vulnerable to the biomedical revolution. The chemical industry is not only vulnerable in the products it sells, but also in the emissions produced from its factories. It also has a substantial problem of land contamination at many of its factories and sites that have been used in the past for operations or dumping waste. One current example is ICI at Runcorn in the UK, where past pollution is becoming current liability, see Box 14 for details.

The chemical industry also has a huge legacy of producing persistent or bioaccumulative chemicals, an unacceptable habit that must be stopped. The biomedical revolution will improve our ability to understand what this contamination is doing to our bodies – and potentially open up new opportunities for legal action against the chemical industry. After all, the entire population of the Earth has been contaminated (see Section 4.3.2).

The industry has got away with selling damaging chemicals and releasing pollution for decades – the biomedical revolution will finally make these activities untenable, and impose substantial costs in clean up and liability.

### Box 13: Monsanto under fire

One company that has been affected by a loss of confidence in its products is Monsanto, a company which saw genetically modified soya as its chance to dominate the world market. However, in spite of spending substantial resources on promoting its products, it has been unable to persuade European consumers to buy them – and they are having growing problems with US consumers.

This has had a substantial impact on their share price – it has fallen from over \$60 in August 1998 to less than \$40 in early 2000. Europe's biggest bank, Deutsch Bank, has advised investors to sell their shares in Monsanto because of the adverse impacts of their GM activities on their share price [139].

To survive these advances the chemical industry must become more forward-looking. It must stop defending old chemicals, and move on. There are real concerns as to whether much of the industry is capable of making these changes.

It appears that the UK industry, in particular, is not investing in the future. A report by the Royal Society of Chemistry concluded that [141]:

*"Overall, the chemical industry has reduced its R&D intensity and appears to depend more on maintaining existing business and less on generating new products and processes. It is less capable of generating new chemicals business in the UK."*

Those companies that adopt the policies laid out in Section 6.1 will have the most chance of surviving fairly unscathed. Those that keep up 'business as usual' will be heading for trouble.

## 5.7 Impacts on consumer products companies

The consumer products industry is responsible for most of the public's chemical exposures. This sector must ensure that it knows what chemicals it is using and why. This is a particular problem in areas of strong commercial confidentiality, such as can lining systems or perfume formulations. New science is likely to lead to more demand for product withdrawals, and an increase in liability actions.

The sector will also need to accept that full openness is necessary, along with a much more precautionary approach to the selection of chemicals (see Section 6.1). Failure to take these steps could lead to severe damage to brands, and loss of confidence in the companies themselves – a loss of corporate reputation (as with Monsanto, Box 13). Consumer products companies – and retailers – depend on public confidence in their name and brands in order to generate loyalty – and this confidence can be a fragile thing. A survey in 1998 by the PR consultants Burson-Marsteller and Wirthlin Worldwide looked at what is important in a corporate reputation, and found that both 'business influentials' and consumers considered the top three attributes to be:

- customer focus;
- quality products/services;
- believability [142].

These three attributes can all be damaged by health concerns about chemicals in products.

The Perrier case (Box 12) is a good example of brand damage, while the case of asbestos (Box 11) is a salutary example of what happens when a severe health effect can be scientifically linked with a product.

### 5.8 Impacts on retailers

Retailers will be presented with pressures similar to those of consumer product manufacturers. New problems will highlight the need for openness and may require the withdrawal of products. Many retailers have been forced to accept the need for openness on genetically modified ingredients – they cannot then claim confidentiality for chemicals in products.

Protection from future problems will come through a commitment to an open, precautionary approach to the use of chemicals – see Section 6.1.

### 5.9 Impacts on shareholders

The above impacts on industry will clearly affect investment returns. Industries that are forward-looking are most likely to remain unscathed, while less aware industries could suffer severe damage to their brands or chemicals they produce. The worst affected are

likely to be in the chemicals sector, where many companies waste their energies defending old chemicals, apparently unaware that the world is changing around them.

Companies that are not taking a sustainable approach to their use of chemicals will suffer in the long term. There is already strong evidence that those companies most committed to good environmental performance are also those with the best quality of management and hence profitability [145].

### 5.10 Impacts on insurers

The insurance industry is the financial back-stop for the above industries. Companies will in general be insured for a range of risks, with the most relevant being:

- product liabilities;
- pollution liabilities;
- health and safety liabilities.

#### Box 14: ICI's pollution catches up with them

The village of Weston, in Cheshire, UK, is situated beside an old quarry. This quarry was filled with 50 years or more of waste from ICI's Runcorn factory nearby, including mercury, chlorinated solvents, chemical catalysts and thousands of unmarked steel drums. ICI has been investigating contamination around the quarry since 1993; in January 2000 they revealed that it had found hexachloro-1,3-butadiene (HCBd), a toxic but poorly understood chemical, in boreholes near the village. Monitoring within the houses of the village followed, and by March, 21 out of 131 properties were found to be contaminated with HCBd, and the residents had been evacuated to local hotels [143].

ICI has already offered to buy affected houses, but it may have to buy many more, due to the complete loss of confidence in the safety of the area. ICI may also be faced with legal actions, and it is still unclear what steps it may have to take to clean up or contain the contamination [144].

Many other chemical companies have similar dumps, dating from the time when there was minimal regulation, and everything was dependant on voluntary commitments from industry. No one knows the extent of these liabilities.

It is important that insurers properly investigate the risks that they are insuring, in particular examining the advances in science described in this report. The history of asbestos claims (Box 11) should serve to warn the industry that once the science is in place, liability cases can be very expensive.

In particular, there are concerns about the level of assessment of risks in product liability insurance:

*"It is by and large true to say that product liability underwriting has in the past been a desk exercise and very few insurers in the UK and Europe had become involved with physical risk assessment and control.....A number of large European insurers do employ specialist engineers and a number of specialist product liability risk assessment organisations do exist. In the future there will perhaps be more involvement by insurers in this respect." [146]*

A cursory assessment of risk will not be financially successful as the biomedical revolution improves the odds in liability cases. The industry must start to assess the risks more thoroughly, to ensure that more risky, backward looking companies pay higher premiums than those more committed to sustainability and a precautionary approach.

Other insurance products will also be affected. Insurance against product withdrawal is particularly vulnerable, as loss of confidence in products and rapid scientific change is likely to lead to an increase in withdrawals. Some insurance companies are also offering 'Reputational Insurance', which is also clearly impacted by problems caused by slow or inadequate reaction to problems with products.

## 6 Solutions

**This report has outlined a range of scientific advances that will cause problems for the regulation of chemical use and exposure. How can the regulatory system – and industry – respond? These scientific advances are happening – and they won't slow down. A robust, precautionary system will minimise the risks to regulators, industry, insurers and investors.**

In Friends of the Earth's opinion, the key solution to the problems posed by the biomedical revolution is risk reduction, both by industry and the regulators.

There needs to be more openness surrounding chemicals use, and a more precautionary approach must be taken to which chemicals are used. Such solutions are in the long term interests of the chemical industry, even though they may cause a few companies some pain in the short term.

The European Commission is currently reviewing the regulation of industrial chemicals – this provides a vital opportunity to transform the current inadequate system into a truly precautionary regulatory process. However, it is in industry's interests to adopt more precautionary policies as soon as possible – it does not have to wait to be forced by the regulator.

### 6.1 Friends of the Earth's proposals

In 1998 Friends of the Earth worked with a range of other environment and health groups in the UK to draw up a simple, two page, statement of what is wrong with chemicals policy, and how can it be improved. The full text is in Annex 1.

Working with other EU NGOs, including the European Environment Bureau, we have formulated a concise description of our requirements from the current EU review of chemicals policy:

**We demand from the EU review of chemicals policy:**

- 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.**

Forward thinking companies will publicly support these proposals and implement them voluntarily. But regulation is essential to ensure that all companies are forced to take a precautionary approach to the use of chemicals.

#### 6.1.1 A full right to know, including what chemicals are present in products

A right to know would ensure that all decisions are transparent, and that consumers are allowed to make their own choices about what they are exposed to.

The right to know is an essential part of a precautionary policy, as it allows both

consumers and industry to make informed decisions about what chemicals they wish to use. It also assists the regulator in their attempts to find out what chemicals are present in particular products. Industry's standard 'commercial confidentiality' argument is invalid, as in reality competitors can use sophisticated analytical techniques if they want to know the composition of a product. The funding for such analysis is not generally available to the public or regulators – so 'commercial confidentiality' is really about keeping the rest of us in the dark.

A right to know would not necessarily mean that all components have to be listed on the label, but that this information would be available on demand. Such information could, for example, be available as a product database on the Internet. Friends of the Earth also recommends that the EU, or Member States, provide an on-line database of information on chemicals safety. This database would ideally incorporate the following:

- levels of information about each chemical, suited to different people, i.e. from a member of the public to a scientist, and including any information about special susceptibilities. The database should include degradation products and impurities.
- hazard data on each chemical, indicating where tests have not been done, and details of its occurrence in the environment or our bodies (e.g. breast milk). Inclusion of health and safety and classification and labelling details for each chemical, would make the database into a full health, safety and environmental database.
- uses and non-hazard properties to allow industry to use the database to select products. For example, a search could be made for a white pigment, suitable for use in food contact materials. This search would generate a list of suitable chemicals, together with their hazard characteristics – facilitating substitution. The manufacturer could then select the least hazardous chemical, and maybe follow a link to the manufacturer or distributor.

Such a database would provide an authoritative source of information on chemicals, and an

effective method of promoting risk reduction. Much of the information already exists in electronic form – for example within the IUCLID database (the EU's main chemicals database). Other information, for example on uses, could be submitted to the database by producers and users using automated methods.

Industry should reveal all results of safety testing of chemicals, whether *in vivo* or *in vitro*. Such information will enable more informed responses to new discoveries by, for example, providing information on what receptors a chemical has been found to bind, or what metabolic pathways are used to inactivate it.

**6.1.2 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**

As described in Section 4.3.1, there is very little information available about the safety of most 'Existing' chemicals. In contrast, all 'New' chemicals placed on the market since 1981 have been assessed for safety, a process that costs industry money. Those selling 'Existing' chemicals have been able to avoid these assessment costs and so these chemicals have a competitive advantage. The use of these unassessed chemicals must be reviewed with a time decided for their removal from the market. This proposal has been supported by a recent brainstorming of individuals from chemical regulatory bodies across Europe [105].

Friends of the Earth propose the following deadlines for submission of hazard characterisation and exposure data:

- 2003 for high production volume chemicals, produced or imported at >1000 tonnes a year;
- 2005 for medium production volume chemicals, produced or imported at between 100 and 1000 tonnes a year;
- 2008 for low production volume chemicals, at <100 tonnes per year.

If data is not complete by these dates, then the chemical must be removed from the market.

A range of methods can be used to speed up hazard characterisation, for example the use of grouping (dealing with similar chemicals together) and quantitative structure - activity relationships (using computer models to predict toxicity). Above all, we must be sure, beyond reasonable doubt, that the uses of chemicals are safe.

The approval of chemicals for uses, or groups of uses, will ensure that more restrictions are placed on more hazardous substances. This doesn't mean that all chemicals need an exhaustive list of approved uses – a chemical with minimal hazards could be approved for 'all uses', a chemical with some environmental hazards might be approved for non diffuse uses, whereas even more hazardous chemicals would have more specific use restrictions and approvals. Approvals must be regularly reviewed to ensure that new discoveries are rapidly incorporated into the regulatory process.

Section 4.3.3 described the problems regulators have in finding out the products chemicals are being used in. There are several possible solutions to this problem, including:

- an obligation on companies using chemicals to notify the company that supplied the chemical of its uses. The supplier of the chemical at the top of the chain would then give this information to the regulator.
- an obligation on companies to submit use information to an automated on-line database, or to have the information available in a standard form on their own web sites.

The chemical industry must be obliged to provide more data, and the industries profiting from the chemicals must bear more of the costs of the risk evaluation process.

Risk evaluation is not an absolute truth, and is affected by the assumptions that are made during the assessment process. Because of this, it must not be carried out by those who have financial interests in the outcome. The chemical producers should finance such assessments, but they should be commissioned and administered through an independent body, preferably the experts ('Competent Authorities') designated by the Member States.

Risk evaluations should also consider the societal need for, and socio-economic impacts of, a product. In situations of inadequate data, a precautionary approach should be taken.

Once chemicals are assessed, the information required to determine the need for substitution and control is available. This information is essential to enable the regulatory system to respond to new science. Approvals for use will enable the regulator to know what chemicals are used for, and enable them to withdraw approval if new information emerges.

### **6.1.3 A phase out of persistent or bioaccumulative chemicals**

All synthetic chemicals in use should break down rapidly into natural substances. There should be no accumulation in the human body, wildlife or the environment. Such accumulation adds to the complexity of our exposure to mixtures of chemicals, and even if we do not currently know that individual chemicals are toxic, there is no way of removing contamination from our bodies and the environment if at some later point they are found to be toxic.

The only exemption would be for chemicals where these hazard properties are an essential function for a specific application.

If individuals are particularly susceptible to the effects of a persistent or bioaccumulative chemical there is likely to be little opportunity for the individual to avoid exposure. Contamination by such chemicals is not acceptable.

### **6.1.4 A requirement to substitute less safe chemicals with safer alternatives**

The EU regulation of industrial chemical use currently contains no requirement on companies to use the safest possible chemicals. Such a requirement does however exist in the Biocides Directive, where comparative assessment must be performed to establish which chemicals are best for any purpose.

There is also a similar responsibility in UK Health & Safety legislation, in the Control of Substances Hazardous to Health (or COSHH) Regulations. If hazardous substances are to be used, if it is reasonably practicable, an employer must prevent exposure by:

- changing the process or activity so that the hazardous substance is not required or generated; or
- replacing it with a safer alternative; or
- using it in a safer form. [147]

The principle was also supported by the UK Royal Commission on Environmental Pollution (RCEP) in their report on Setting Environmental Standards [148]:

*“We consider that the criterion of comparison with the risk presented by other available substances should be introduced into all regulatory procedures for the marketing and use of chemicals, including those covering reactants and intermediates.”*

Some Member States have implemented the substitution principle in their chemicals policy, notably Sweden [149]. It has also been proposed in a recent brainstorming of individuals from chemicals regulatory bodies across Europe [105].

Friends of the Earth believes that a mandatory requirement to substitute is an important part of a precautionary policy, and would reduce potential problems arising from discoveries in genetic susceptibility.

Friends of the Earth considers that positive approval of chemicals for uses, with the safest chemical being approved for a use, is the most effective way of enforcing substitution.

A less complex mechanism would be a 'duty to substitute' enforced by a regulator:

Companies have a duty to use the safest and best available chemical or technique for any application. An appeal mechanism is set up whereby an individual or organisation (e.g. competitor supplier, NGO) can appeal to the regulator if they consider that the duty is not being carried out. Some products are likely to be covered by the developing EU Integrated Products Policy, others could be subject to comparative assessment, and the regulator could publish a 'list of undesirable chemicals' for more straightforward substitutions.

Lack of an available substitute should not be used as an excuse for delaying a ban on a

chemical that is unsafe; all use of chemicals must be safe beyond reasonable doubt.

An obligation to substitute will ensure that the safest possible chemicals – or techniques – are used. This reduces the chances that the chemicals will be identified as a problem by advances in science.

### **6.1.5 A commitment to stop all releases to the environment of hazardous substances by 2020**

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 agreement on cleaning up the north-east Atlantic. Hazardous substances are defined in the OSPAR Convention as substances that are persistent, bioaccumulative and toxic, or which give rise to similar levels of concern. By reducing environmental contamination, this commitment will also reduce risks from new science. In addition, it is worth noting that genetic susceptibilities will also exist in wildlife, and might be particularly important in small, isolated, threatened populations.

## **6.2 Why use a precautionary approach?**

Friends of the Earth considers that a precautionary approach is essential for dealing with uncertain science and lack of knowledge. Precaution is a way of incorporating scientific uncertainties into the regulatory system, as described in a recent report for the EU Forward Studies Unit [150]:

*“Rather than seeing ‘precaution’ as being in tension with ‘science based regulation’, research conducted under this project suggests that key elements of a precautionary approach are entirely consistent with sound scientific practice in responding to intractable problems in risk assessment such as ‘ignorance’ (“we don’t know what we don’t know”) and ‘incommensurability’ (“we have to compare apples and pears”)...The acknowledgement of such difficulties under a precautionary approach may thus be seen as a more scientifically rigorous way of carrying forward the regulation of technological risk than would be their denial under a purely ‘risk-based’ approach.”*

The European Commission's recent Communication on the precautionary principle (see Section 5.5) has stated that the precautionary principle "*is a central plank of Community policy*".

### **6.3 The regulator's responsibility**

The regulator has a responsibility to create a regulatory system that provides a high level of protection for both people and the environment. It also has a responsibility to ensure the regulatory system is capable of responding to scientific developments.

The regulatory changes described above will create a more robust, open and precautionary regulatory system that will be more able to cope with advancing science than the current system, which is based on secrecy and ignorance. Modifying the regulatory system cannot happen instantaneously, but changes must be made to cope with the advances described in this report.

The regulator must regulate – it is not acceptable to abdicate responsibility to industry. Industry has its responsibilities, which are often coloured by its own economic motivations, but the regulator has been placed in position as a public authority to protect the public and the environment.

The chemical industry has shown little interest in true precautionary production and use of chemicals. For example, it continues to fight controls on any chemicals such as hormone disrupting alkylphenols [151] and breast milk contaminating brominated flame retardants [152]. A limited programme of hazard testing of some chemicals does not solve the problems caused by inadequate regulations and an advancing understanding of the effects of chemicals on the body. Industry needs to be forced forward by legislation – it has had years to take voluntary action, and it has failed.

#### **6.3.1 EU level**

Within Europe the EU industrial chemicals regulatory process is the key tool available for creating a more precautionary system. Unfortunately, it takes a long time to change EU regulations. A new Directive will take a minimum of five years to come into force. By then, advances in biomedical science will be exposing problems, the more serious problems emerging towards the end of the decade. Work

must begin now to deal with this technology – there is a real danger of regulations being overtaken by science.

The review of EU regulations currently underway, provides an opportunity – given the timing, the only opportunity – to create a robust, precautionary, system, as described above.

#### **6.3.2 UK level**

The UK Government has recently completed its review of chemicals policy [153]. Unfortunately, the resulting strategy is very conservative, relying almost entirely on voluntary action from the chemical industry, an industry with a very poor record. Such a strategy will not begin to deal with the problems coming from the biomedical revolution.

The UK should be pushing for the above precautionary policies at EU level, but unfortunately the Government's approach seems to be driven by short sighted pro chemical industry policies, which will damage the industry in the long term.

#### **6.3.3 Globally**

The USA is ahead of the EU in funding research on genetic susceptibilities, but their regulatory system will have the same problems that the EU faces. The challenge of creating a new, precautionary and transparent system will also need to be faced in the USA.

Efforts so far in global chemical control have been limited, with the main focus currently on the Persistent Organic Pollutants treaty, which only initially covers 12 chemicals. Those living outside the EU have the same rights to protection from chemicals as EU citizens. More powerful and precautionary control of chemicals use is required at a global level, to ensure that the chemical industry is prevented from selling dangerous chemicals everywhere, not just in industrialised countries. Everyone is entitled to protection from harm from chemicals.

#### **6.3.4 A need for more research and understanding**

New biomedical research will throw up new problems and concerns, some of which will initially be uncertain or confused. It is

important for regulators to invest in scientific research to better understand these concerns.

In addition, regulators also need to better characterise human exposures to chemicals, particularly during key developmental phases, for example by carrying out comprehensive analysis of chemicals contaminating breast milk. Such research will facilitate detection of chemicals of concern, including those that may be produced as impurities or breakdown products, and might otherwise be ignored.

#### 6.4 The responsibility of industry

Industry has a responsibility to ensure that its products are safe for all. It also has a responsibility to its shareholders to provide profits in the long term. The biomedical revolution threatens both these responsibilities for those companies that do not take a precautionary approach to their use of chemicals, as laid out above. In particular:

- the chemical industry must review the chemicals it produces, and abandon those which are persistent or bioaccumulative. It must ensure that it knows how hazardous the chemicals are, and what they are used for. It must move away from more hazardous chemicals in favour of low or minimal hazard chemicals, and clean up discharges from its factories, dealing with any legacy of contaminated land. The penalty for ignoring these problems will be loss of market for products, and a substantial increase in the risk of damaging liability actions;
- the consumer product industry must adopt the policies in Section 6.1, becoming far more aware of what chemicals it is using in products, and ensuring that the safest possible chemicals – or techniques – are used. It must also have a total commitment to openness. The risks of brand damage, product withdrawals and liability actions are increasing, and too dangerous to ignore;
- retailers must quiz their suppliers to ensure that they are taking a precautionary approach with the use of chemicals in their products. Retailers should be aware if any chemicals which are already under suspicion are in products they are selling, and put pressure on their suppliers to substitute if possible;
- investors need to be aware of the potential losses that could come from one of the companies they are investing in being hit by concerns about a chemical it makes or uses. Product withdrawals and liability actions can be hugely expensive – and damage to brand value may never be recovered. It is in their own interests to pressurise companies to adopt a precautionary approach to the use of chemicals – not a 'head in the sand' or conservative approach;
- insurers must ensure that they know what they are insuring, particularly in the case of cover for product liability, withdrawal and reputational cover. Risk must be fully assessed, incorporating possible future developments, and insurers should work with companies to manage those risks by moving to more precautionary use of chemicals. Increasingly successful liability cases will take a toll on those insurers who are not aware of the problems – no insurer wants to end up insuring another asbestos, or even anything close.

#### 6.5 The perils of inaction

This report predicts the future challenges for the regulation and use of chemicals. Without a radical reform of both, there will be further major problems for those who regulate and use chemicals, including:

- a further loss of public confidence in chemicals;
- a further loss of confidence in the competence of regulators;
- expensive product recalls or drops in sales;
- expensive liability actions.

The next few years provide industry and the regulators with a window of opportunity to move to a more precautionary approach. The advance in science is relentless – the biomedical revolution will not stop. Now is the time to act to ensure that confidence in the regulator and industry is possible in the future.

**Don't say we didn't warn you.**

# 7 Annex 1: The Joint Statement on Chemicals and Health

## September 1998

We welcome the UK Government's review of the 'Sustainable Production and Use of Chemicals' and the review of chemical legislation within the European Union. The following statement has been agreed by the signatories named below:

***We are concerned that:***

(i) the majority of chemicals in current use have not had adequate toxicity testing. The European Environment Agency has stated that about 75% of the approximately 2500 chemicals in large scale use (whose production in the EU exceeds 1,000 tonnes) have not got sufficient toxicity data publicly available for even a preliminary toxicity assessment;

(ii) chemicals which bioaccumulate and persist in the human body and the environment are still in routine use;

(iii) increasing numbers of chemicals are being shown to disrupt the function of the endocrine, immune and nervous systems of both humans and animals;

(iv) most exposures to chemicals occur as mixtures, rather than individual chemicals, but little consideration is given to this in the regulation of chemicals;

(v) some parts of the human population are far more susceptible to chemical exposures, including developing foetuses, babies, children and those with certain genetic variants. Animals show similar variation in susceptibility;

(vi) the incidences of breast cancer, testicular cancer and asthma have increased dramatically over the past few decades and there is concern that these increases may be linked to exposure to chemicals.

We believe that a more sustainable chemicals policy is both necessary and possible. It should include policies which will more adequately protect both the public's health and the health of the environment.

A sustainable chemical strategy should focus on reducing the risks posed by chemicals, and it should be guided by the precautionary principle. The complexities described above mean that uncertainty is pervasive when evaluating the effects of chemicals, even if considerable resources are spent on research. We propose that a new strategy should include the following elements:

***(i) A positive licensing system***

Chemicals regulation should move towards being a positive licensing system, where chemicals are licensed for different uses, in the same way as already occurs for pesticides and pharmaceuticals. Industry should have to demonstrate that these licensed applications of chemicals are safe beyond reasonable doubt, and that society has a need for them. The potential impacts on the environment of discharges of a chemical should be fully evaluated prior to licensing.

***(ii) The elimination of persistent or bioaccumulative chemicals***

All synthetic chemicals in use should break down rapidly into harmless, natural substances. There should be no accumulation in the human body, wildlife or the environment, unless this is an essential function in a specific application. Phasing out persistent and/or bioaccumulative chemicals will reduce exposures.

**(iii) The phase out of dangerous chemicals**

Those existing chemicals that do not fulfil the above requirements should be phased out as soon as possible, and at least by 2010. The Government should ensure that all Persistent Organic Pollutants (POPs) covered by the United Nations Economic Commission for Europe protocol on POPs are phased out well before this deadline.

**(iv) Substitution of toxic chemicals**

Where a less toxic chemical is available for an application, it should be substituted for the more toxic chemical. This is the 'substitution principle'.

**(v) Minimising the quantity of chemicals used**

The minimum necessary quantity of chemicals should be used for any application.

**(vi) Producer liability**

Liability for the effects of chemicals should rest with the producer of the chemicals concerned, not with the general public.

**(vii) The right to know**

The public should have a right to know what chemicals are present in any product they use, including in the packaging of the product. The public should also have access to information on the safety of all chemicals. This information will help individuals to make informed choices.

**(viii) The elimination of marine pollution**

The Government must adhere to its commitment to cease all discharges of hazardous chemicals to the marine environment by 2020, as agreed in the Sintra Statement arising from the Ministerial Meeting of the Oslo and Paris Commission in July 1998.

The strategy outlined above will improve protection of both human health and the environment. It will also reduce the burden of dealing with the poorly-characterised existing chemicals, as many chemicals will be withdrawn from use. Such a strategy will also improve the occupational environment by replacing more toxic chemicals with less toxic ones.

These proposals do not threaten the survival of the chemical industry, they merely call for the production of better chemicals.

We must take action now; the massive expansion of the production and use of synthetic chemicals since the 1930s has been undertaken with insufficient regard for the health of humans and the environment – now we have the chance to protect people and the environment from the effects of dangerous chemicals.

**Signatories include:**

Friends of the Earth (England, Wales and Northern Ireland), Friends of the Earth (Scotland), World Wide Fund For Nature (WWF) UK, UNISON, Women's Environmental Network (WEN), Scottish Wildlife Trust, Marine Conservation Society, SERA (the Labour Environment Campaign), Association for Public Health, Hyperactive Children's Support Group, Association for Spina Bifida and Hydrocephalus, Food and Chemical Allergy Association, Action Against Allergy, The Pesticides Trust, Wildfowl and Wetlands Trust, International Wildlife Coalition, Confederation of Indian Organisations (UK) and The Food Commission.

## 8 References

1. Wilson, E.O., *Consilience: The unity of knowledge*, 1998. Little, Brown and Company, London.
2. Elsea, S.H. and P.I. Patel, 'Organization of the Human Genome, Chromosomes and Genes', in *Principles of Molecular Medicine*, J.L. Jameson, Editor, 1998, Humana Press, Totowa, New Jersey, USA, p. 3-7.
3. Mueller, R.F. and I.D. Young, *Emery's Elements of Medical Genetics*, 10th ed, 1998. Churchill Livingstone, Edinburgh.
4. Human Genome Program, *Primer on Molecular Genetics*, 1992, US Department of Energy, Washington, D.C.  
[http://www.ornl.gov/TechResources/Human\\_Genome/publicat/primer/intro.html](http://www.ornl.gov/TechResources/Human_Genome/publicat/primer/intro.html)
5. Dickson, D. and M. Wadman, 'Genome effort 'still in need of support'', *Nature*, 1998, 393: p. 201.
6. Butler, D., 'US/UK statement on genome data prompts debate on 'free access'', *Nature*, 2000, 404: p. 324-325.
7. Wadman, M., 'Human Genome Project aims to finish 'working draft' next year', *Nature*, 1999, 398: p. 177.
8. Little, P., 'The book of genes', *Nature*, 1999, 402: p. 467-468.
9. Human Genome Project, *Researchers decode three human chromosomes (Press Release)*, April 13th 2000.  
<http://www.ornl.gov/hgmis/project/51619jgi.html>
10. Dunham, I., N. Shimizu, B.A. Roe, and S. Chissole, 'The DNA sequence of human chromosome 22', *Nature*, 1999, 402: p. 489-495.
11. Zimmern, R.L., 'The human genome project: a false dawn?', *British Medical Journal*, 1999, 319: p. 1282-1284. Full issue available free online at <http://www.bmj.com/>
12. Butler, D., 'IBM joins genomics mapping consortium', *Nature*, 2000, 403: p. 473.
13. Woodman, R., 'Wellcome Trust and drug giants fund gene marker database', *British Medical Journal*, 1999, 318: p. 1093.
14. Dodson, M. and R. Williamson, 'Indigenous peoples and the morality of the Human Genome Diversity Project', *Journal of Medical Ethics*, 1999, 25: p. 204-208.
15. Smaglik, P., 'Genetic diversity project fights for its life...', *Nature*, 2000, 404: p. 912.
16. EHP, 'Environmental genome project advances', *Environmental Health Perspectives*, 1997, 105: p. 1298.
17. Abbott, A., 'A post-genomic challenge: learning to read patterns of protein synthesis', *Nature*, 1999, 402: p. 715-720.
18. Burley, S.K., S.C. Almo, J.B. Bonanno, M. Capel, M.R. Chance, T. Gaasterland, D. Lin, A. Sali, F.W. Studier, and S. Swaminathan, 'Structural genomics: beyond the Human Genome Project', *Nature Genetics*, 1999, 23: p. 151-157.
19. IBM, *IBM unveils \$100 million research initiative to build world's fastest supercomputer (Press Release)*, December 6th 1999. Available at <http://www.ibm.com/news/1999/12/06.phtml>
20. Matsunami, H., J.-P. Montmauear, and L.B. Buck, 'A family of candidate taste receptors in human and mouse', *Nature*, 2000, 404: p. 601-604.
21. Lander, E.S., 'Array of hope', *Nature Genetics*, 1999, 21 Suppl. 1: p. 3-4. Available free at [http://library.genetics.nature.com/server-java/Propub/genetics/ng0199supp\\_3.pdf](http://library.genetics.nature.com/server-java/Propub/genetics/ng0199supp_3.pdf)
22. Strachan, T. and A.P. Read, *Human Molecular Genetics*, 2nd ed, 1999. Bios, Oxford, UK.
23. Singh-Gasson, S., R.D. Green, Y. Yue, C. Nelson, F. Blattner, M.R. Sussman, and F. Cerrina, 'Maskless fabrication of light-directed oligonucleotide microarrays using a digital micromirror array', *Nature Biotechnology*, 1999, 17: p. 974-978.
24. Lee, C.K., R.G. Klopp, R. Weindruch, and T.A. Prolla, 'Gene expression profile of ageing and its retardation by caloric restriction', *Science*, 1999, 285: p. 1390-1393.
25. Abbott, A., 'Alliance of US labs plans to build map of cell signalling pathways', *Nature*, 1999, 402: p. 219-220.
26. Medlin, J., 'New microscope gives scientists the inside scoop on living cells', *Environmental Health Perspectives*, 1999, 107.

27. Mark, D.H. and R.M. Glass, 'Impact of new technologies in medicine. A global theme issue', *Journal of the American Medical Association*, 1999, 282: p. 1875. Full issue available free at <http://jama.ama-assn.org/issues/v282n19/toc.html>
28. Berger, A. and R. Smith, 'New technologies in medicine and medical journals', *British Medical Journal*, 1999, 319. Full issue available free online at <http://www.bmj.com/>
29. Stephenson, J., 'Lab-on-a-chip shows promise in defining and diagnosing cancers', *Journal of the American Medical Association*, 1999, 282: p. 1801-1802. Available free at <http://jama.ama-assn.org/issues/v282n19/pdf/jmn1117.pdf>
30. Allzadeh, A.A., M.B. Elsen, D.A. Davis, C. Ma, I.S. Lossos, A. Rosenwald, J.C. Boldrick, H. Sabet, T. Tran, J.I. Powell, L. Yang, and et al, 'Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling', *Nature*, 2000, 403: p. 503-511.
31. Sanger Centre, *A revolutionary project to identify cancer genes (Press Release)*, 20th October 1999, The Sanger Centre. <http://www.sanger.ac.uk/Info/Press/991020.shtml>
32. Walker, A.H., D. Najarian, D.L. White, J.M. Jaffe, P.A. Kanetsky, and T.R. Rebbeck, 'Collection of genomic DNA by buccal swabs for polymerase chain reaction-based biomarker assays', *Environmental Health Perspectives*, 1999, 107: p. 517-520.
33. Sadée, W., 'Pharmacogenomics', *British Medical Journal*, 1999, 319: p. 1286-1289. Full issue available free online at <http://www.bmj.com/>
34. Meek, J., 'Development of gene test drugs pose ethics dilemma', in *The Guardian*, London, UK, 14th April 2000, p. 1. [http://www.newsunlimited.co.uk/uk\\_news/story/0,3604,162530,00.html](http://www.newsunlimited.co.uk/uk_news/story/0,3604,162530,00.html)
35. Glaxo Wellcome, *New approaches to drug registration need to be considered to keep pace with genetic research (Press Release)*, April 14th 2000. [http://www.glaxowellcome.co.uk/news/press\\_release/mn\\_PR955703483.html](http://www.glaxowellcome.co.uk/news/press_release/mn_PR955703483.html)
36. Cookson, C., 'No charity given when science is at stake', in *The Financial Times*, London, UK, 18th November 1999.
37. British Medical Association, *Human Genetics: Choice and Responsibility*, 1998. Oxford University Press, Oxford.
38. HGAC, *The Implications of Genetic Testing for Employment*, 1999, Human Genetics Advisory Commission, London. <http://www.dti.gov.uk/hgac/papers/paperg1.htm>
39. Williamson, R., 'What's 'new' about 'genetics'?', *Journal of Medical Ethics*, 1999, 25: p. 75-76.
40. BBC, 'Clinton bans DNA job tests', in *BBC News online* 8th February 2000. [http://news.bbc.co.uk/hi/english/world/americas/newsid\\_635000/635881.stm](http://news.bbc.co.uk/hi/english/world/americas/newsid_635000/635881.stm)
41. Vainio, H., 'Use of biomarkers - new frontiers in occupational toxicology and epidemiology', *Toxicological Letters*, 1998, 102-103: p. 581-589.
42. Perera, F.P., W. Jedrychowski, V. Rauh, and R.M. Whyatt, 'Molecular epidemiologic research on the effects of environmental pollutants on the fetus', *Environmental Health Perspectives*, 1999, 107 Suppl. 3: p. 451-460.
43. Farr, S. and R.T. Dunn, 'Concise review: Gene expression applied to toxicology', *Toxicological Sciences*, 1999, 50: p. 1-9.
44. Medlin, J.F., 'Timely technology', *Environmental Health Perspectives*, 1999, 107: p. A256-A258.
45. Cockerill, M., 'Online research archive will be free to all', *Nature*, 1999, 402: p. 721-722.
46. Delamothe, T., 'BMJ set to sign with PubMed Central, JSTOR, and WorldSpace', *British Medical Journal*, 2000, 320: p. 8. Available free at <http://www.bmj.com/>
47. Smith, R., 'Millennium, what millennium?', *British Medical Journal*, 2000, 320: p. 1. Available free at <http://www.bmj.com/>
48. Butler, D., 'Brussels research chief backs European website proposal', *Nature*, 2000, 403: p. 124.
49. Eysenbach, G., E. Ryoung Sa, and T.L. Diepgen, 'Shopping around the internet today and tomorrow: towards the millennium of cybermedicine', *British Medical Journal*, 1999, 319: p. 1294-1298. Full issue available free online at <http://www.bmj.com/>
50. Shannon, K., 'Genetic predispositions and childhood cancer', *Environmental Health Perspectives*, 1998, 106 Suppl. 3: p. 801-806.
51. Weber, W.W., *Pharmacogenetics*, 1997. Oxford University Press, Oxford.
52. Nelson, N.J., 'Genetic profiling for cancer surfaces slowly in the clinic', *Journal of the National Cancer Institute*, 1999, 91: p. 1990-1992.
53. Wolf, C.R., G. Smith, and R.L. Smith, 'Pharmacogenetics', *British Medical Journal*, 2000, 320: p. 987-990. <http://www.bmj.com/cgi/content/full/320/7240/987>

54. Nature Biotechnology, 'Make biology compulsory for presidential candidates', *Nature Biotechnology*, 1999, 17: p. 831.
55. Sipes, I.G. and A.J. Gandolfi, 'Biotransformation of toxicants', in *Casarett and Doull's Toxicology: The Basic Science of Poisons*, 4th ed, 1991, Pergamon Press, New York, p. 88-126.
56. Omiecinski, C.J., R.P. Rimmel, and V.P. Hosagrahara, 'Concise review of the cytochrome P450s and their roles in toxicology', *Toxicological Sciences*, 1999, 48: p. 151-156.
57. Daly, A.K., K.S. Fairbrother, and J. Smart, 'Recent advances in understanding the molecular basis of polymorphisms in genes encoding cytochrome P450 enzymes', *Toxicological Letters*, 1998, 102-103: p. 143-147.
58. Lewis, D., 'Sex and drugs and P450', *Chemistry & Industry*, 1997: p. 831-834.
59. Hu, X., C. Herzog, P. Zimniak, and S.V. Singh, 'Differential protection against benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide-induced DNA damage in HepG2 cells stably transfected with allelic variants of pi class human glutathione S-transferase.', *Cancer Research*, 1999, 59: p. 2358-2362.
60. van Lieshout, E.M.M., H.M.J. Roelofs, S. Dekker, C.J.J. Mulder, T. Wobbes, J.B.M.J. Jansen, and W.H.M. Peters, 'Polymorphic expression of the Glutathione S-transferase P1 gene and its susceptibility to Barrett's esophagus and esophageal carcinoma', *Cancer Research*, 1999, 59: p. 586-589.
61. Srám, R.J., 'Effect of glutathione S-transferase M1 polymorphisms on biomarkers of exposure and effects', *Environmental Health Perspectives*, 1998, 106 Suppl. 1: p. 231-239.
62. Bennett, W.P., M.C.R. Alavanja, B. Blomeke, K.H. Vähäkangas, K. Castrén, J.A. Welsh, E.D. Bowman, M.A. Khan, D.B. Fleider, and C.C. Harris, 'Environmental tobacco smoke, genetic susceptibility, and risk of lung cancer in never-smoking women', *Journal of the National Cancer Institute*, 1999, 91: p. 2009-2014.
63. El-Masri, H.A., D.A. Bell, and C.J. Portier, 'Effects of glutathione transferase theta polymorphism on the risk estimates of dichloromethane to humans', *Toxicology and Applied Pharmacology*, 1999, 158: p. 221-230.
64. Board, P., A. Blackburn, L.S. Jermiin, and G. Chelvanayagam, 'Polymorphism of phase II enzymes: identification of new enzymes and polymorphic variants by database analysis', *Toxicological Letters*, 1998, 102-103: p. 149-154.
65. Brockmüller, J., I. Cascorbi, R. Kerb, C. Sachse, and I. Roots, 'Polymorphisms in xenobiotic conjugation and disease predisposition', *Toxicological Letters*, 1998, 102-103: p. 173-183.
66. Thompson, P.A., F. Seyedi, N.P. Lang, S.L. MacLeod, G.N. Wogan, K.E. Anderson, Y.-M. Tang, B. Coles, and F.F. Kadlubar, 'Comparison of DNA adduct levels associated with exogenous and endogenous exposures in human pancreas in relation to metabolic genotype', *Mutation Research*, 1999, 424: p. 263-274.
67. Huang, C.S., H.D. Chern, C.Y. Shen, S.M. Hsu, and K.J. Chang, 'Association between N-acetyltransferase 2 (NAT2) genetic polymorphism and development of breast cancer in post-menopausal Chinese women in Taiwan, an area of great increase in breast cancer incidence.', *International Journal of Cancer*, 1999, 82: p. 175-179.
68. Hein, D.W., M.A. Doll, A.J. Fretland, M.A. Leff, S.J. Webb, and G.H. Xiao, 'Molecular genetics and epidemiology of the NAT1 and NAT2 acetylation polymorphisms', *Cancer Epidemiology, Biomarkers & Prevention*, 2000, 9: p. 29-42.
69. Haley, R.W., S. Billecke, and B.N. La Du, 'Association of low PON1 type Q (Type A arylesterase activity with neurologic symptom complexes in Gulf War veterans', *Toxicology and Applied Pharmacology*, 1999, 157: p. 227-233.
70. Akgür, S.A., P. Öztürk, E.Y. Sözmen, Y. Delen, T. Tanyalçin, and B. Ege, 'Paraoxonase and acetylcholinesterase activities in humans exposed to organophosphorus compounds', *Journal of Toxicology and Environmental Health part A*, 1999, 58: p. 469-474.
71. Costa, L.G., W.F. Li, R.J. Richter, D.M. Shih, A. Lulis, and C.E. Furlong, 'The role of paraoxonase (PON1) in the detoxification of organophosphates and its human polymorphism', *Chemico-Biological Interactions*, 1999, 119-120: p. 429-438.
72. Au, W.A., C.H. Sierra-Torres, N. Cajas-Salazar, B.K. Shipp, and M.S. Legator, 'Cytogenetic effects from exposure to mixed pesticides and the influence from genetic susceptibility', *Environmental Health Perspectives*, 1999, 107: p. 501-505.
73. Krajcinovic, M., D. Labuda, C. Richer, S. Karimi, and D. Sinnett, 'Susceptibility to childhood acute lymphoblastic leukemia: Influence of CYP1A1, CYP2D6, GSTM1, and

- GSTT1 genetic polymorphisms.', *Blood*, 1999, 93: p. 1496-1501.
74. Longuemaux, S., C. Deloménie, C. Gallou, A. Méjean, M. Vincent-Viry, R. Bouvier, D. Droz, R. Krishnamoorthy, M.M. Galteau, C. Junien, C. Bérout, and J.M. Dupret, 'Candidate genetic modifiers of individual susceptibility to renal cell carcinoma: A study of polymorphic human xenobiotic-metabolizing enzymes.', *Cancer Research*, 1999, 59: p. 2903-2908.
  75. Hubble, J.P., J.H. Kurth, S.L. Glatt, M.C. Kurth, G.D. Schellenberg, R.E.S. Hassanein, A. Leiberman, and W.C. Koller, 'Gene-toxin interaction as a putative risk factor for Parkinson's disease with Dementia', *Neuroepidemiology*, 1998, 17: p. 96-104.
  76. Sabbagh, N., A. Brice, D. Marez, A. Dürr, M. Legrand, J.-M.L. Guidice, A. Destée, Y. Agid, and F. Broly, 'CYP2D6 Polymorphism and Parkinson's disease susceptibility', *Movement Disorders*, 1999, 14: p. 230-236.
  77. Edelson, S.B. and D.S. Cantor, 'Autism: Xenobiotic influences', *Toxicology and Industrial Health*, 1998, 14: p. 553-563.
  78. Bartsch, H., M. Rojas, U. Nair, J. Nair, and K. Alexandrov, 'Genetic susceptibility and DNA adducts: Studies in smokers, tobacco chewers, and coke oven workers', *Cancer Detection and Prevention*, 1999, 23: p. 445-453.
  79. ENDS, 'Massive hormone screening exercise proposed by USA', *ENDS Report*, 1998, 278: p. 8.
  80. vom Saal, F.S., P.S. Cooke, D.L. Buchanan, P. Palanza, K.A. Thayer, S.C. Nagel, S. Parmigiani, and W.V. Welshons, 'A physiologically based approach to the study of bisphenol a and other estrogenic chemicals on the size of reproductive organs, daily sperm production, and behavior', *Toxicology and Industrial Health*, 1998, 14: p. 239-260.
  81. Spearow, J.L., P. Doemeny, R. Sera, R. Leffler, and M. Barkley, 'Genetic variation in susceptibility to endocrine disruption by estrogen in mice', *Science*, 1999, 285: p. 1259-1261.
  82. Long, X., R. Steinmetz, N. Ben-Jonathan, A. Caperell-Grant, P.C.M. Young, K.P. Nephew, and R.M. Bigsby, 'Strain differences in vaginal responses to the xenoestrogen bisphenol a', *Environmental Health Perspectives*, 2000, 108: p. 243-247.
  83. Taylor, J.A., B.M. Judy, B.A. Rottinghaus, K.J. Blackwell, G.E. Rottinghaus, L.C. Alworth, F.S. vom Saal, and W.V. Welshons, 'Bisphenol a bioaccumulates in the serum of pregnant mice', presented at 'Environmental Hormones: Past, Present, Future', October 18th-20th 1999, Tulane University, USA.
  84. Rebbeck, T.R., P.W. Kantoff, K. Krithivas, S. Neuhausen, M.A. Blackwood, A.K. Godwin, M.B. Daly, S.A. Narod, J.E. Garber, H.T. Lynch, B.L. Weber, and M. Brown, 'Modification of *BRCAl*-associated breast cancer risk by the polymorphic androgen-receptor CAG repeat', *American Journal of Human Genetics*, 1999, 64: p. 1371-1377.
  85. Ross, R.K., G.A. Coetzee, C.L. Pearce, J.K.V. Reichardt, P. Bretsky, L.N. Kolonel, B.E. Henderson, E. Lander, D. Altshuler, and G. Daley, 'Androgen metabolism and prostate cancer: Establishing a model of genetic susceptibility', *European Urology*, 1999, 35: p. 355-361.
  86. Kelce, W.R., C.R. Stone, S.C. Laws, L.E. Gray, J.A. Kemppainen, and E.M. Wilson, 'Persistent DDT metabolite p, p'-DDE is a potent androgen receptor antagonist', *Nature*, 1995, 375: p. 581-585.
  87. Ecobichon, D.J., J.E. Davies, J. Doull, M. Ehrich, R. Joy, D. McMillan, R. MacPhail, L.W. Reiter, W. Slikker, and H. Tilson, 'Neurotoxic effects of pesticides', in *The effects of pesticides on human health, proceedings of a workshop May 9-11, Colorado, Advances in modern environmental toxicology, Volume XVIII*, S.R. Baker and C.F. Wilkinson, Editors, 1990, Princeton Scientific Publishing, New Jersey, USA.
  88. Gallagher, G. and M. Seldin, 'Welcome to 'Genes and Immunity'', *Genes and Immunity*, 1999, 1: p. 1-2.
  89. van der Pouw Kraan, T.C.T.M., A. van Veen, L.C.M. Boeije, S.A.P. van Tuyl, E.R. de Groot, S.O. Stapel, A. Bakker, C.L. Verweij, L.A. Aarden, and J.S. van der Zee, 'An IL-13 promoter polymorphism associated with increased risk of allergic asthma', *Genes and Immunity*, 1999, 1: p. 61-65.
  90. Kleeberger, S.R., R.C. Levitt, L.-Y. Zhang, M. Longphre, J. Harkema, A. Jedlicka, S.M. Eleff, D. DiSilvestre, and K.J. Holroyd, 'Linkage analysis of susceptibility to ozone-induced lung inflammation in inbred mice', *Nature Genetics*, 1997, 17: p. 475.
  91. EHP, 'Genes and ozone', *Environmental Health Perspectives*, 1998, 106.
  92. Cooper, G.S., F.W. Miller, and J.P. Pandey, 'The role of genetic factors in autoimmune disease: Implications for environmental research', *Environmental Health Perspectives*, 1999, 107 Suppl. 5: p. 693-700.
  93. Shackelford, R.E., W.K. Kaufmann, and R.S. Paules, 'Cell cycle control, checkpoint

- mechanisms, and genotoxic stress', *Environmental Health Perspectives*, 1999, 107: p. 5-24.
94. Alexander, B.H., H. Checkoway, P. Costa-Mallen, E.M. Faustman, J.S. Woods, K.T. Kelsey, C. van Metten, and L. Costa, 'Interaction of blood lead and  $\delta$ -aminolevulinic acid dehydratase genotype on markers of heme synthesis and sperm production in lead smelter workers', *Environmental Health Perspectives*, 1998, 106: p. 213-216.
  95. Onalaja, A.O. and L. Claudio, 'Genetic susceptibility to lead poisoning', *Environmental Health Perspectives*, 2000, 108 Suppl. 1: p. 23-28.
  96. Mottershead, D., 'Integrated pollution prevention and control', in *Preparing for changes in chemical control in 2000*, 1999, London, UK, Charles Simeons Conferences.
  97. European Commission, *What do Europeans think about the environment. The main results of the survey carried out in the context of Eurobarometer 51.1.*, 1999, Commission of the European Communities, Brussels, Belgium.  
<http://europa.eu.int/comm/environment/barometer/index.htm>
  98. European Commission, *Report on the operation of Directive 67/548/EEC, Directive 88/379/EEC. Regulation (EEC) 793/93 and Directive 76/769/EEC*, 1999, European Commission, Brussels.
  99. Agency, E., *What's in your backyard - 1998 Pollution Inventory*, 1999, Environment Agency, England and Wales.  
<http://193.122.103.90/wiyby/html/introduction.htm>
  100. Pearce, F., 'A heavy responsibility', in *New Scientist*, London, UK, 27th July 1996, p. 12-13.
  101. European Chemicals Bureau data, 1999.
  102. EEA, *Chemicals in the European Environment: Low Doses, High Stakes?*, 1998, European Environment Agency. Available free at  
<http://themes.eea.eu.int/toc.php/issues/chemicals?doc=35878&l=en>
  103. Ahrens, A., *What is wrong with EU's Chemicals Policy*, 1999, European Environment Bureau, Brussels.
  104. Allanou, R., B.G. Hansen, and Y. van der Bilt, *Public availability of data on EU High Production Volume chemicals*, 1999, European Chemicals Bureau, Ispra, Italy.  
<http://ecb.ei.jrc.it/Data-Availability-Documents/datavail.pdf>
  105. EU Chemicals Regulators, *Future European Chemicals Policy: Report Brainstorming session 16-17 December 1999*, 1999, Ministry of Housing, Spatial Planning and the Environment, The Netherlands.
  106. CSTEE, *Minutes of the 11th plenary meeting of the Scientific Committee on toxicity, Ecotoxicity and the Environment (CSTEE), 27-28 September 1998*, 1999, European Commission. At  
[http://europa.eu.int/comm/dg24/health/sc/sct/ou52\\_en.html](http://europa.eu.int/comm/dg24/health/sc/sct/ou52_en.html)
  107. Lyons, G., *Toxic Trespass*, 1999, WWF. Executive summary available on the web at  
<http://www.wwf-uk.org/news/chem4.pdf>
  108. Cooper, I. and W. Summerfield, *Survey of BADGE epoxy monomer in canned foods*, 1997, UK Ministry of Agriculture, Fisheries and Food.
  109. Soto, A.M., C. Sonnenschein, K.L. Chung, M.F. Fernandez, N. Olea, and F.O. Serrano, 'The E-SCREEN assay as a tool to identify estrogens: An update on estrogenic environmental pollutants', *Environmental Health Perspectives*, 1995, 103: p. 113-122.
  110. Niesink, R.J.M., J. de Vries, and M.A. Hollinger, eds. *Toxicology: principles and applications*, 1996, CRC Press, Boca Raton, USA.
  111. Crome, P., 'The elderly', in *Risk assessment strategies in relation to population subgroups*, 1999, Institute for Environment and Health, Leicester, UK, p. 27-28.
  112. Goehl, T.J., 'Playing in the sand', *Environmental Health Perspectives*, 1997, 105.
  113. Buffler, P.A. and A.D. Kyle, 'Carcinogen risk assessment guidelines and children', *Environmental Health Perspectives*, 1999, 107: p. A286-A288.
  114. Khattak, S., G. K-Moghtader, K. McMartin, M. Barrera, D. Kennedy, and G. Koren, 'Pregnancy outcome following gestational exposure to organic solvents: A prospective controlled study.', *Journal of the American Medical Association*, 1999, 281: p. 1106-1109.
  115. Government-Research Councils Initiative on Risk Assessment and Toxicology, *Risk assessment strategies in relation to population subgroups*, 1999, Institute for Environment and Health, Leicester, UK.
  116. Renwick, 'Human variability and risk assessment/safety assurance', in *Risk assessment strategies in relation to population subgroups*, 1999, Institute for Environment and Health, Leicester, UK, p. 13-14.

117. ENDS, 'Chemicals policy in the melting pot', *ENDS Report*, 1999, 297: p. 34-38.
118. ENDS, 'EU backs down on leaded petrol ban', in *ENDS Daily*, London, UK, 20th December 1999.
119. UK Creutzfeld-Jacob Disease Surveillance Unit, *CJD Statistics*, 2000, UK Creutzfeld-Jacob Disease Surveillance Unit, <http://www.cjd.ed.ac.uk/figures.htm>
120. The BSE Inquiry, *Frequently Asked Questions (FAQs)*, 2000, The BSE Inquiry. <http://www.bse.org.uk/>
121. Almond, J. and J. Pattison, 'Human BSE', *Nature*, 1997, 389: p. 437-438.
122. Scott, M.R., R. Will, J. Ironside, H.-O.B. Nguyen, P. Tremblay, S.J. DeArmond, and S.B. Pruisner, 'Compelling transgenic evidence for transmission of bovine spongiform encephalopathy prions to humans', *Proceedings of the National Academy of Sciences USA*, 1999, 96: p. 15137-15142.
123. Thornton, J. and S. Tromans, 'Human Rights and Environmental Wrongs. Incorporating the European Convention on Human Rights: Some thoughts on the consequences for UK Environmental Law', *Journal of Environmental Law*, 1999, 11: p. 35-57.
124. Care, A., "Dangerous *per se*?", *Chemistry & Industry*, 1998, 22: p. 932.
125. Ball, S. and S. Bell, *Environmental Law*, 3rd ed, 1991. Blackstone Press Ltd, London, UK.
126. European Commission, *Product Safety: Liability for defective products*, 1999, European Commission. <http://europa.eu.int/scadplus/leg/en/lvb/132012.htm>
127. Albin, M., C. Magnani, S. Krstev, E. Rapiti, and I. Shefer, 'Asbestos and cancer: An overview of current trends in Europe', *Environmental Health Perspectives*, 1999, 107 Suppl. 2: p. 289-298.
128. Reuters, 'British T&N falls once more under asbestos shadow', in *Reuter News Service - United Kingdom*, London, UK, 1995.
129. Economist, 'The grim reaper', in *The Economist Europe Intelligence Wire*, London, UK, 4th November 1995.
130. Peto, J., A. Decarli, C. La Vecchia, F. Levi, and E. Negri, 'The European mesothelioma epidemic', *British Journal of Cancer*, 2000, 79: p. 666-672.
131. McClintick, D., 'The decline and fall of Lloyd's of London', *Time Europe*, 2000, 155. <http://www.pathfinder.com/time/europe/magazine/2000/221/lloyds.html>
132. Heuston, R.F.V. and R.A. Buckley, *Salmond and Heuston on the Law of Torts*, 20th ed, 1992. Sweet & Maxwell Ltd, London, UK.
133. Economist, 'Management Brief. When the bubble burst', in *The Economist Europe Intelligence Wire*, London, UK, 3rd August 1991.
134. Telegraph, 'Summertime set to stage sparking water wars: French fight to put fizz back in sales as rivals pour into market gap left by Perrier's eau-no', in *Daily Telegraph Europe Intelligence Wire*, London, UK, 29th June 1990.
135. Reuters, 'Perrier drops veteran chairman as benzene scare costs bite', in *Reuters News Service - Western Europe*, London, UK, 29th June 1990.
136. Grocer, 'Low Water Mark - Perrier Sales', in *Grocer/ Reuter Textline*, UK, 5th February 1994.
137. European Commission, *Communication from the Commission on the Precautionary Principle*, 2000, Commission of the European Communities, Brussels, Belgium. [http://europa.eu.int/comm/off/com/health\\_consumer/precaution.htm](http://europa.eu.int/comm/off/com/health_consumer/precaution.htm)
138. European Commission, *Green Paper: Liability for defective goods*, 1999, Commission of the European Communities, Brussels, Belgium. <http://europa.eu.int/comm/dg15/en/update/consumer/99-580.htm>
139. Brown, P. and J. Vidal, 'GM investors told to sell their shares', in *The Guardian*, London, UK, 25th August 1999, p. 1.
140. European Commission, *White Paper on Environmental Liability*, 2000, Commission of the European Communities, Brussels, Belgium. <http://europa.eu.int/comm/environment/liability/index.htm>
141. Brophy, J., *The impact of chemicals industry mergers, acquisitions and restructuring on the UK chemistry infrastructure*, 2000, Royal Society of Chemistry, London, UK. <http://www.rsc.org/pdf/general/m&auk.pdf>
142. Burson-Marsteller, *Maximising corporate reputation*, 1998, Burson-Marsteller. [http://www.bm.com/files/insights/flash/mcr\\_index.html](http://www.bm.com/files/insights/flash/mcr_index.html)
143. Bromley, A., *Letter from ICI to residents: Project pathway weekly update 4*, 23rd February 2000.
144. Vidal, J., 'Village of the damned: How ICI poisoned a Cheshire community', in *The Guardian G2*, London, UK, 11th February 2000, p. 1-3.

- <http://www.newsunlimited.co.uk/g2/story/0,3604,135452,00.html>
145. FM Research, *Capital Punishment: UK Insurance companies and the global environment*, 2000, Friends of the Earth, London, UK.
  146. Thomas, D.A., 'Product Liability Insurance', in *European Product Liabilities*, 2nd ed, P. Kelly and R. Attree, Editors, 1997, Butterworths, London, p. 541-555.
  147. UK Health and Safety Executive, *COSHH: the new brief guide for employers. Guidance on the main requirements of the Control of Substances Hazardous to Health (COSHH) Regulations 1994*, 1998.  
<http://www.open.gov.uk/hse/pubns/coshh2.htm>
  148. RCEP, *Setting Environmental Standards*, 1998, Royal Commission on Environmental Pollution, London, UK.
  149. KEMI, *The Environmental Code*, 1999.  
<http://www.miljo.regeringen.se/pressinfo/pdf/eng1.pdf>
  150. Stirling, A., *On science and precaution in the management of technological risk*, 1999, Science Policy Research Unit, University of Sussex, Brighton, UK.
  151. ENDS, 'US manufacturers attack NPE phase-out proposals', *ENDS Report*, 1999, 298: p. 45.
  152. ENDS, 'Industry admits flame retardant pollution, resists phase-out', *ENDS Report*, 1999, 298: p. 13-14.
  153. DETR, *Sustainable Production and Use of Chemicals - A Strategic Approach*, 1999, UK Department of the Environment, Transport and the Regions, London, UK.  
<http://www.environment.detr.gov.uk/chemistrat/index.htm>