

Hazardous Chemicals Management

The Issue

Chemicals are widely recognised to be important to health and modern lifestyles. Their continued use is essential for GlaxoSmithKline to produce medicines and other products that positively impact the quality of human life. Chemicals are used at every stage in pharmaceutical production. They are necessary to enable us to carry out fundamental research into the causes of disease, in the discovery of new medicines, in the manufacture of active pharmaceutical ingredients (API's) and in the formulation of our products. The types of chemicals used include reagents, catalysts, solvents, acids and bases, intermediates, surfactants, colours and flavourings and wide variety of excipients.

Many legal requirements have been introduced into international legislation over the years to protect people and the environment from the potential adverse effects of exposure to hazardous chemicals. However, although significant reductions in pollution from major industrial sources have been made, basic information on the public health and environmental hazards of many chemicals placed on the market for use in manufacturing processes and in everyday products is still lacking [1]. Moreover, advances in analytical technology have shown that many of these chemicals have widespread distribution in the environment and can be found in human tissues [2]. These factors have reinforced each other and contributed to heightened societal concern about chemicals and doubts about the effectiveness of the regulatory systems to anticipate and prevent unacceptable human health and environmental impacts [3]. This has in turn led to developments in governmental chemicals policy such as the proposed EU Registration, Evaluation and Authorisation of Chemicals Regulation (REACH) [4].

GlaxoSmithKline Position

GSK is a global company whose mission is "to improve the quality of human life by enabling people to do more, feel better and live longer". In order to carry out fundamental research into the causes of human disease and to make and deliver our medicines to the patient we are dependent on a large variety of chemicals. However we recognise that, to be consistent with our stated mission, hazardous chemicals must be used in a way that minimises any potential adverse effects on human health or the environment.

We therefore support the 2002 Johannesburg World Summit target to "use and produce chemicals in ways which will lead to the minimisation of significant adverse effects on human health and the environment by 2020".

We believe that the effective management of hazardous chemicals must be based upon an understanding of the risk they present. Any hazardous chemical used in our research activities is handled in small quantities under strictly controlled conditions that minimise any emissions or exposure and therefore does not represent a significant risk to human health or the environment. Consequently the research phase of our product lifecycle is not included in the scope of this position statement. The focus of which is chemicals used in larger quantities such as, during clinical development, in manufacturing operations and in our marketed products. The issue of pharmaceuticals in the environment is the subject of a separate public position statement and consequently pharmaceutical actives are not considered in the scope of this document.

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GlaxoSmithKline's Position

Based upon intrinsic hazard we consider managing the risks presented by the following classes of chemicals to be a priority in reaching our sustainability goals: those known to be carcinogens, mutagens or reproductive hazards (CMR's), those known to be toxic and bioaccumulate or persist in the environment (PBT's), those known to be very persistent or very bioaccumulative in the environment (vPvB), ozone depleting chemicals, endocrine disruptors and those known to cause asthma (*see definitional criteria in Appendix 1*)

We believe that a focus on five priority areas will help to ensure that the chemicals we produce or use do not adversely affect human health or the environment:

1.) Hazard Assessment and Communication

A good understanding of intrinsic hazard is critical for decision making and the sound management of chemicals. Therefore we:

- Continue to use assessment approaches that identify the key environmental, health and safety (EHS) hazards associated with all GSK chemicals
- Implement robust processes to obtain EHS information on non-proprietary chemicals from our suppliers and published literature
- Provide relevant stakeholders (e.g. employees, contract manufacturers/key suppliers, customers, regulators etc) with chemical hazard information to enable them to adopt appropriate risk management approaches

2.) Substitution of "Hazardous Chemicals"

We have adopted a chemicals management approach that applies the substitution principle as the initial alternative, where this can be achieved without compromising our ability to deliver valuable therapies to patients. To that end we:

- Identify "priority chemicals" that we currently use, using the criteria in Appendix 1
- Actively assess the feasibility of using alternative, less hazardous chemicals
- Focus on the development phase of new products to identify when and where these less hazardous chemicals may be used
- Replace "priority chemicals" in our existing products and manufacturing processes, if this is technically and economically feasible
- Adopt appropriate risk management approaches where elimination or substitution is not possible

3.) Transparency

We are committed to openness and transparency about how we manage hazardous chemicals and will continue to engage with relevant stakeholders and make the following information publicly available:

- What we consider to be a "priority chemical"
- Progress on initiatives designed to eliminate or substitute "priority chemicals"
- Information on risk management strategies developed to support continued use of any "priority chemical"
- Environment, Health & Safety data on our products



4.) Supply Chain Management

We believe that we should play a role in encouraging responsible management of hazardous chemicals throughout our supply chain and apply consistent standards to our contract manufacturing operations. This can be achieved by:

- Requiring that our suppliers comply with all legal and regulatory requirements
- Establishing global EHS requirements for key suppliers and contract manufacturers and where appropriate conducting pre-contract EHS evaluations of potential suppliers
- Conducting periodic audits against these requirements and where necessary providing encouragement and assistance to help contract manufacturers and key suppliers to improve their EHS performance
- Including robust EHS management systems and "responsible care" programmes in the criteria for the selection of key suppliers and contract manufacturers of priority chemicals

Selected EHS performance metrics for key suppliers and contract manufacturers will be reported in the GSK Sustainability in Environment, Health & Safety Annual report

5.) Sustainable Chemistry

We believe that the principles of green chemistry play an important role in the management of hazardous chemicals [5]. Therefore we will continue efforts to identify opportunities to adopt sustainable chemical technologies including:

- Improving process design and efficiency to minimise the use of chemicals and reduce associated waste or emissions
- Identifying opportunities to use less hazardous chemicals and ensuring any residual risks are appropriately managed
- Exploring opportunities for the use of renewable resources and biotransformations
- Using inherently safer chemistry
- Minimising energy- and water-intensive manufacturing processes
- Exploring and optimising recycling and reuse opportunities

Key performance metrics relating to sustainable chemistry will be developed and reported in the GSK Sustainability in Environment, Health & Safety Annual report

Background

GlaxoSmithKline (GSK) is a research-based healthcare company. Our headquarters are in the UK and we have a significant presence in the US. GSK's mission is to improve the quality of human life by enabling people to do more, feel better and live longer. Based on 2004 Annual Results, we had a turnover of £20 billion (\$36 billion) and profit before tax of £6 billion (\$11 billion) which represents an estimated seven per cent of the world's pharmaceutical market.

GSK has leadership in four major therapeutic areas: anti-infectives; central nervous system (CNS); respiratory and gastro-intestinal/metabolic. In addition, we are a leader in the important area of vaccines and have a growing portfolio of oncology products. We also have a Consumer Healthcare portfolio comprising over-the-counter (OTC) medicines, oral care products and nutritional healthcare drinks.

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GlaxoSmithKline's Position

The use of chemicals is an essential prerequisite to undertake fundamental research into human disease. Chemicals are also required in the discovery and development phases of new pharmaceutical products, the chemical synthesis and manufacturing of pharmaceutical actives and the formulation of pharmaceutical and consumer healthcare products. Therefore GSK is a significant user of chemicals.

The manufacture, transport and supply of chemicals and their use in our operations are governed by a substantial body of legislation enacted to protect health & safety and the environment. For example over the last 40 years, the EU has generated more than 500 Directives and associated instruments relating to chemicals and consumer protection, occupational health, environmental protection, process and transport safety and hazardous substance management. Through our Global EHS Standards, we are committed to identifying regulatory requirements and ensuring full compliance. Moreover, where a GSK operation is subject to both GSK and regulatory requirements, the stricter requirement will apply.

In addition to regulatory compliance, GSK is committed to the principle of product stewardship and has an active "green chemistry" programme aimed at developing more sustainable manufacturing processes. This has achieved significant results in minimising the use of hazardous chemicals. For example in 2004 a team of chemists from the GSK Chemical Development site in Tonbridge won the prestigious AstraZeneca Award for Excellence in Green Chemistry and Engineering at the UK IChemE Awards for process improvements that had significant environmental benefits associated with a medicine in development. In addition to green chemistry initiatives we have been successful in substituting hazardous chemicals from our product portfolio. This is exemplified by our commitment to phase-out use of CFC's from our metered dose inhalers for asthma.

The pharmaceuticals sector is unique in that, quite rightly, there are very strict regulatory and quality requirements imposed to ensure that any changes in manufacturing do not adversely affect the safety or efficacy of the medicine. This means that before considering the substitution of an existing process chemical we must ensure that any replacement fits with the chemistry of the manufacturing process and validate that the change has not affected the efficacy or patient safety profile of the medicine. Consequently, it may not be technically feasible to substitute chemicals in many existing processes and even if it were possible the cost of making such changes can be prohibitive. The result of this dilemma is that success with substitution or elimination of hazardous chemicals from synthetic routes, formulations and products is likely to be focused on new product development activities.

Further Background Information

1. Allanou R., Hansen BG., and van der Bilt Y (1999). Public availability of data on EU high production volume chemicals. EU 18996 EN European Chemicals Bureau, Ispra, Italy
2. Thornton JW., McCally M., and Houlihan J (2002). Biomonitoring of Industrial Pollutants: Health and Policy Implications of the Chemical Body Burden. Public Health Reports 117, 315-323
3. Royal Commission on Environmental Pollution. Twenty-fourth Report. Chemicals in Products; Safeguarding the Environment and Human Health. June 2003



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4. European Commission (2001) Strategy for a future chemicals policy. COM (2001)88. Brussels: European Commission
5. Green Chemistry: Theory and Practice. Paul Anastas and John Warner. Oxford University Press. 1998

Approved January 2006

A publication of Corporate Environment, Health & Safety



**Appendix 1:
Criteria for classification as a “Priority Chemical”**

Carcinogen (C)

A substance that fulfils the following EC criteria for Category 1 or 2 carcinogen (i.e., R45 or R49):

- Category 1: A substance known to be carcinogenic in humans. There is sufficient evidence to establish a causal link between human exposure and the development of cancer
- Category 2: A substance that should be regarded as if it were carcinogenic to humans. There is sufficient evidence to provide a strong presumption that human exposure may result in the development of cancer on the basis of:
 - a) Appropriate long term animal studies
 - b) Other relevant information

Mutagen (M)

A substance that fulfils the following EC criteria for Category 1 or 2 mutagen (ie R46):

- Category 1: A substance known to be mutagenic in humans. There is sufficient evidence to establish a causal link between human exposure and heritable genetic damage
- Category 2: A substance that should be regarded as if it were mutagenic to humans. There is sufficient evidence to provide a strong presumption that human exposure may result in the heritable genetic damage on the basis of:
 - a) Appropriate animal studies
 - b) Other relevant information

Reproductive Hazard (R)

A substance that fulfils the following EC criteria for Category 1 or 2 reproductive hazard (ie R60, R61)

- Category 1: A substance known to impair fertility or to cause developmental toxicity in humans. There is sufficient evidence to establish a causal link between human exposure and impaired fertility or subsequent developmental toxic effects in progeny
- Category 2: A substance that should be regarded as if could impair fertility or cause developmental toxicity to humans. There is sufficient evidence to provide a strong presumption that human exposure may result in impaired fertility or subsequent developmental toxic effects in progeny on the basis of:
 - a) Clear evidence in animal studies of impaired fertility in the absence of toxic effects or clear evidence of developmental effects in the absence of marked maternal toxicity
 - b) Other relevant information

Asthmagen

A substance that fulfils the following EC criteria for substances that may cause sensitisation by inhalation (ie R42):

- If there is evidence that the substance or preparation can induce specific respiratory hypersensitivity or
- Where there are positive results from appropriate animal studies or
- If the substance is an isocyanate, unless there is evidence that the substance does not cause respiratory hypersensitivity

PBT

A substance that fulfils all three criteria of the sections below is a PBT Substance

Persistence

- The half-life in marine water is higher than 60 days, or
- The half life in fresh or estuarine water is higher than 40 days, or
- The half life in marine sediment is higher than 180 days, or
- The half life in fresh or estuarine water sediment is >120 days, or
- The half life in soil is >120 days.

Bioaccumulation

- Bioconcentration factor >2000

Toxicity

- NOEC for marine or freshwater organisms <0.01mg/l
- Substance is classified as carcinogenic (category 1 or 2- see above), mutagenic (category 1 or 2-see above) or toxic to reproduction (category 1 or 2 –see above)
- There is evidence of chronic toxicity (classified as T, R48 or Xn, R48 according to Directive 67/548/EEC)

vPvB

A substance that fulfils the following criteria:

Persistence

- The half-life in marine, fresh or estuarine water is higher than 60 days, or
- The half-life in marine, fresh or estuarine water sediment is higher than 180 days, or
- The half life in soil is >180 days.

Bioaccumulation

- Bioconcentration factor >5000

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GlaxoSmithKline's Position

Ozone depleting chemical

A substance that fulfils the following EC criteria for dangerous to the ozone layer (ie R59):

- Substances which on the basis of predicted or observed environmental fate and behaviour may present a danger to the structure and/or functioning of the stratospheric ozone layer

Endocrine disruptor

Endocrine disrupters have been defined as exogenous substances that alter function(s) of the endocrine system and consequently cause adverse health effects in an intact organism, or its progeny, or (sub) populations. These will be identified on a case by case basis as no definitive or validated tests currently exist to help identification of such chemicals.

Approved January 2006

A publication of Corporate Environment, Health & Safety

