

**Policy Department
Economic and Scientific Policy**

The benefits of strict cut-off criteria on human health in relation to the proposal for a Regulation concerning plant protection products

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Executive Summary

This study assesses the health benefits of strict ‘cut-off criteria’ on human health in relation to the proposal for a Regulation concerning the placing of plant protection products on the market (COM(2006) 388). The Common Position text provides that active substances classified as *carcinogen, mutagen or toxic for reproduction category 1 or 2* (CMR 1 & 2), or substances considered to have *endocrine disrupting properties* (ED) on the basis of internationally agreed test guidelines, shall not be approved unless exposure to humans under realistic proposed conditions of use would be negligible.

The European Parliament in its first reading amendments proposed the additional criteria that substances “considered to cause a risk of *developmental neurotoxic or immunotoxic properties* in humans, taking into account exposure during embryonic/foetal life and/or during childhood as well as likely combination effects” should only be approved if human exposure would be negligible.

In view of the continuing debate about the criteria for approval of active substances, this study provides a scientific review of evidence concerning human health effects of plant protection products, including health benefits that could accrue from the stricter cut-off criteria. The study supports the proposal of the European Parliament that in order to ensure added protection of human health, substances considered to cause a risk of developmental neurotoxic or immunotoxic effects in humans should be added to the list of classifications that would result in non-approval of active substances, unless negligible exposure can be demonstrated. The emerging epidemiological evidence for these effects will need to be translated into classification criteria before harmonised classification for these effects can be achieved.

Given that many CMR3 substances may be reclassified at a future point as CMR2, the additional proposal of the European Parliament to include CMR3 as criteria for toxicity in the case of persistent, bioaccumulating and toxic (PBT) substances and for defining substances as candidates for substitution deserves strong consideration.

The study focuses on the adverse effects of long-term exposures. It notes that exposure to pesticides may be occupational, domestic or through the diet. Workers are potentially exposed to higher levels than the general population, and many of the epidemiological studies reporting adverse health effects relate to occupationally exposed individuals. Young children can be exposed to pesticides through their diet and parental occupation, in particular farming, may also be a key exposure pathway. They may be particularly vulnerable to potential adverse health impacts due to the fact that their bodies are still developing, and that protective mechanisms such as metabolic pathways are immature.

It has been suggested that combination effects of pesticides may underlie the epidemiological findings of adverse effects in human populations, including young children, but few toxicological studies have been done on mixtures of active ingredients. Particular attention should be given to exposure during embryonic/foetal life and/or during childhood as well as possible combination effects.

The epidemiological evidence for health impacts associated with chronic pesticide exposure includes various types of cancer, reproductive dysfunction, disruption of the endocrine, immune or neural systems, respiratory disease and cognitive disability. In relation to cancer, positive associations have been reported between household or occupational pesticide exposure and various types of cancer, including leukaemia, brain tumours, Wilm's tumour, non-Hodgkin's lymphoma, sarcomas, and prostate cancer. In particular, children's and pregnant women's exposure to pesticides has been positively associated with cancers both in childhood and later in adult life.

A number of studies have found the risk of childhood cancers to be higher amongst the children of workers in agriculture and children living on farms, with a particularly strong association for childhood brain tumours. Considerable difficulty exists however in proving an association between exposure to a specific pesticide and occurrence of cancer, particularly in a context where people may have been exposed to multiple substances, including non-pesticide agents.

Associations between pesticide exposure and adverse reproductive outcomes include gynaecological and endocrine dysfunction. Studies have linked pesticide exposure, both maternal and paternal, with adverse pregnancy outcomes such as miscarriage, preterm birth, SGA, stillbirth, neonatal death, foetal distress, and sex ratio. Reported effects on child development after *in utero* exposures have included developmental delay, retarded growth parameters and various malformations, including hydrocephaly, vascular malformations, and anophthalmia. A number of pesticides can affect endocrine function in laboratory experiments and in wildlife. Endocrine disruption may be an underlying cause of at least some reproductive disorders.

Several classes of pesticides, including the organophosphate compounds are known to have acute neurotoxic effects on humans. However, recent studies have identified a number of links between chronic, low-dose exposures and long term neurological problems, including neurodegenerative diseases; functional nervous system impacts, including cognitive problems; mental and emotional impact; and developmental neurotoxicity, i.e., impacts on foetuses and young children caused by exposure to certain chemicals during critical moments of brain development. For example, a strong link has been found between pesticide exposure and Parkinson's disease.

In relation to developmental neurotoxicity, although the causes of many neurodevelopmental disorders are mostly unknown, during foetal development and through early childhood the developing brain is particularly susceptible to the adverse effects of neurotoxicants. Studies of children diagnosed with autism spectrum disorders (ASDs) in California found a significant association between mother's residential distance from sites of agricultural pesticide application and the stage of gestation at the time of pesticide use.

Finally, some pesticides are immunotoxic in experimental animal studies, and a growing body of epidemiological studies also document pesticide-related effects in the immune systems of humans. Pesticide-associated immune system effects include hypersensitivity reactions (ranging from dermatitis to asthma or anaphylaxis); suppression or stimulation of immune system function and cancers of the immune cell lines.

Most of the potential health benefits from restricting the use of certain pesticides would accrue through avoiding the costs of health impacts associated with pesticide exposure. These costs could include health service costs, the value of an individual's lost quality of life, the value of a statistical life lost due to a pesticide-related death, or loss of productivity (days of work lost) due to a pesticide-related poisoning, whether acute or chronic. To give an idea of the scope of the benefits that could be achieved by reducing pesticide exposure, a 2001 World Bank study estimated that in established market economies pollution from agro-industrial chemicals and chemical pollution from diffuse sources caused between 0.6% and 2.5% of the burden of disease (deaths and general ill health) with a central estimate of 1.5%.

Very few studies have taken on the challenge of estimating economic benefits in terms of reduced costs from chronic health effects linked to specific chemicals, because of the difficulty in showing causation due to exposure. However, a new study for the UK Pesticides Safety Directorate uses an innovative methodology to estimate the benefits of withdrawal of approvals for seven active substances as ranging from £93 to £186 million in potential cancer cases avoided for spray operators only, to £354 to £709 million for the maximum exposed farm worker population, over the relevant exposure period of 30 years (RPA, 2008). These figures are for the UK only. If expressed in Euros and extrapolated to the EU population as a whole (which is roughly 8 times the size of the UK), the benefits of withdrawing approvals for those substances could have an upper bound range of €3,568 to €7,160 billion over the coming 30 years for the maximum exposed farm worker population.

Given the above findings, the following conclusions are reached:

- 1. Hazard-based cut-off criteria are justified where a preventive approach is needed.* Although substance-specific epidemiology studies are lacking for several substances that would be affected by the cut-off criteria, the absence of evidence of effects does not equate to absence of effects. Accumulation of firm evidence can take many years, because of the long latency periods between low-level exposures and some health impacts. In the absence of such evidence and where negligibility of exposure cannot be assured, hazard-based criteria are important tools for prevention.
- 2. The proposed cut-off criteria reflect the seriousness of associated health effects.* The health impacts associated with low-level chronic pesticide exposure are serious. The cut-off criteria reflect this and address the increasingly strong emerging evidence that certain chemicals can interact with the physiological systems of living organisms, including those of humans, resulting in altered function and adverse health effects costly to society.
- 3. The special vulnerability of children argues for extreme caution with respect to developmental neurotoxicants.* Strong associations have been found between neurological problems in children and exposure to pesticides during critical periods of brain development. Recalling the decades it took to gather sufficient evidence of the neurotoxic effects of lead to bring about policy action, and noting the accumulating evidence concerning impacts of neurotoxicant and immunotoxicant pesticides, the developmental neurotoxic and immunotoxic parameters also appear to be warranted.
- 4. The cut-off criteria will provide additional protection for farmers and their families.* Farmers, agricultural workers and their children are at higher risk of incurring health problems due to long-term exposures to pesticides. The fact that the people responsible for producing Europe's food must carry this disproportionate risk and the subsequent costs needs to be balanced against any risks of increased food production costs due to reduced availability of certain pesticides.
- 5. Initial economic analysis indicates potential benefits are significant; more economic analysis needed.* An extensive body of scientific work has found statistically sound evidence of strong associations between exposures to pesticides as a group and to specific substances. However, robust economic analyses of the actual costs of chronic exposures are still missing. A body of economic analysis similar to that carried out for REACH is now needed to provide more solid information on the current costs to society of the health impacts from exposure to certain chemicals used for plant protection, as well as the benefits of reducing such exposures.

1. Introduction

The Committee on Environment, Public Health and Food Safety (ENVI) of the European Parliament has requested an impact assessment on the benefits of strict 'cut-off criteria' on human health in relation to the proposal¹ for a Regulation concerning the placing of plant protection products on the market (COM(2006) 388).

A cornerstone of the draft proposal is that the decision on acceptability or non-acceptability of plant protection substances should be taken at Community level on the basis of harmonised criteria as laid down in Chapter II and points 2 and 3 of Annex II of the proposal, applied by all Member States. Under Article 4(1) of the Regulation an active substance will only be approved if, taking into account these harmonised criteria, the plant protection products (PPP) containing that active substance will fulfil the conditions laid down in Article 4(2) and 4(3).

The text of the Common Position now provides that active substances classified under Directive 67/548/EEC² as carcinogen category 1 or 2, mutagen category 1 or 2, or toxic for reproduction category 1 or 2 ("CMR 1 & 2"), or substances considered to have endocrine disrupting ("ED") properties on the basis of internationally agreed test guidelines, shall not be approved unless exposure to humans under realistic proposed conditions of use would be negligible.³ These are the so-called "cut-off criteria".

During the first reading of the proposed Regulation, the European Parliament proposed a range of amendments to the proposal, including the additional cut-off criterion that substances "considered to cause a risk of developmental neurotoxic or immunotoxic properties in humans, taking into account exposure during embryonic/foetal life and/or during childhood as well as likely combination effects" should only be approved if exposure to humans under realistic conditions of use would be negligible (as is the case for CMR category 1 and 2 in the common position).⁴

The political agreement reached on 23 June 2008 by the European Council does not include this additional cut-off criterion. In view of the continuing debate about the criteria for approval of active substances, there is a need for a systematic scientific review of evidence concerning human health effects of plant protection products, including health benefits that could accrue from the stricter cut-off criteria.

Through consumption of pesticide residues in particular, individuals are exposed to mixtures of active substances. Such mixtures allow synergistic effects to develop between compounds and can lead to enhanced toxicity levels. The long time periods over which exposure takes place, variations in individual vulnerability and the synergistic affects of exposure to multiple substances in the everyday environment make analysis of the human health impacts of individual substances extremely complex. Proving a causal association between a specific substance and long-term illness such as neural and immune disorders is particularly challenging. The lack of precise and corroborated data on the health effects of exposure to many active substances generates uncertainty regarding the benefits of limiting their access to the market.

It is crucial to state that to date none of the impact assessments carried out with respect to the proposed Regulation have fully considered the health impacts of plant protection products. The Commission Staff Working Document reporting on the impact assessment for the Regulation (SANCO/10273/2006 Rev.5) considered different policy options, including comparative assessment of PPPs, but did not look at approval criteria specifically.

¹ COM(2006) 388, as modified by the EP first reading, the Commission's amended proposal COM(2008) 93 and the political agreement from the Council.

² To note: a common position has been reached on a new Regulation on Classification, Labelling and Packaging of Substances and Mixtures which implements the Globally Harmonised System of Classification and Labelling in the EU. This Regulation, which will replace Directive 67/548/EEC, is likely to be published in the Official Journal in November or December, and will come into force 20 days after publication.

³ The granting of approval on the basis of negligible exposure does not apply to active substances classified as mutagen category 1 or 2, since such substances are considered to present a risk to health at any level of exposure.

⁴ The Parliament in its first reading also proposed to include active substances classified under Directive 67/548/EEC as CMR category 3 within the criteria for PBT substances (Annex II, 3.7.2), specifically as "Toxic", whereas the common position only includes Reproductive category 3. Both groups of substances are candidates for substitution under the EP proposal.

Health and environmental impacts were considered only briefly, and from a qualitative point of view. An impact assessment carried out by the UK Pesticides Safety Directorate in May 2008 looked at 283 substances to see which would be affected by the cut-off criteria for health and environmental hazards proposed by the Commission as well as by the more stringent cut-off criteria proposed by the European Parliament. The UK assessment did not consider possible benefits in terms of human health or environment, but rather focused on the possible impact on agricultural productivity if certain chemicals were no longer available for pesticide use.

This study draws on extensive scientific studies to review the epidemiological evidence for health impacts associated with chronic pesticide exposure. It also reviews the possible approaches that have been made to estimate benefits from reductions in chemical exposure, while recognising the difficulties in establishing concrete estimates of causality due to pesticides. The study then ventures several conservative assumptions, on the basis of which estimates are developed of the health benefits of implementing the cut-off criteria as set out in the Common Position, as well as the benefits that might accrue from the additional cut-off criteria proposed by the European Parliament.

2. The cut-off criteria and the active substances involved

As indicated above, the current text of the proposed Regulation provides that active substances classified under Directive 67/548/EEC as carcinogen category 1 or 2, mutagen category 1 or 2, or toxic for reproduction category 1 or 2 (“CMR 1 & 2”), or those considered to have endocrine disrupting (“ED”) properties on the basis of internationally agreed test guidelines, shall not be approved unless exposure to humans under realistic proposed conditions of use would be negligible. The European Parliament proposes to include substances “considered to cause a risk of developmental neurotoxic or immunotoxic properties in humans, taking into account exposure during embryonic/foetal life and/or during childhood as well as likely combination effects”.

It should be noted that the cut-off criteria in the proposed Regulation are based on intrinsic hazard, which is the foundation of classification under Directive 67/548/EEC, whereas the criteria used in the

current Directive 91/414 concerning plant protection products use risk assessment as the basis for approval of active substances. Industry representatives and some Member State officials have stated that such strict cut-off criteria do not have a scientific basis because they are based on intrinsic hazard and not on risk considerations. Others point out that the criteria have been established on the basis of scientific considerations and in the case of certain substances intrinsic hazard to human health has been considered sufficient reason for restrictions under Community law.⁵

2.1 Classification of substances as carcinogenic, mutagenic, or toxic for reproduction

Annex VI of Directive 67/548/EEC contains clear criteria for classification of substances (including pesticide active ingredients) as carcinogenic, mutagenic or toxic for reproduction, categories 1, 2 and 3. These classification criteria are appended as Annex

I of this report. As can be seen from these criteria, classification in one of the 3 categories is based on the strength of evidence for effects in humans, category 1 being assigned when there is clear human evidence, category 2 being used for substances which should be regarded as carcinogenic/mutagenic/reproductively toxic for man and category 3 for substances “which cause concern for man owing to possible CMR effects but in respect of which the available information is not adequate for making a satisfactory assessment”.

Annex II of this report provides a list of the substances that might be excluded on the basis of the cut-off criteria for CMR category 1 and 2 and substances considered to have endocrine-disrupting effects (on the basis of internationally agreed test guidelines).

Box 1: The cut-off criteria and the end points involved

In order to ensure added protection of human health, substances considered to cause a risk of developmental neurotoxic or immunotoxic effects in humans should be added to the list of classifications that would result in non-approval of active substances, unless negligible exposure can be demonstrated.

The emerging epidemiological evidence for these effects will need to be translated into classification criteria before harmonised classification for these effects can be achieved.

Given that many CMR3 substances may be reclassified at a future point as CMR2, the additional proposal of the European Parliament to include CMR3 as criteria for toxicity in the case of persistent, bioaccumulating and toxic (PBT) substances and for defining substances as candidates for substitution deserves strong consideration.

⁵ See Directive 2005/90/EC of the European Parliament and of the Council amending, for the 29th time, Council Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations (substances classified as carcinogenic, mutagenic or toxic to reproduction — C/M/R).

An important point to note is that substances are very often placed in Category 3 for these endpoints when the available evidence and toxicological data are insufficient to justify classification in category 1 or 2. In relation to carcinogenic substances, Annex VI of Directive 67/548/EEC states that Category 3 actually comprises 2 subcategories:

- (a) substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in category 2. Additional experiments would not be expected to yield further relevant information with respect to classification;
- (b) substances which are insufficiently investigated. The available data are inadequate, but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

The same principle applies to classification of category 3 mutagens and reproductive toxicants. Thus, a number of category 3 CMR substances (in category (b)) could ultimately be classified in category 2 or even 1. Classification as a category 1 or 2 mutagen, as covered by the cut-off criteria of the proposed Regulation, requires proof of heritable effects that are transmissible to the offspring, while classification as a category 3 mutagen requires only demonstration of genotoxic effects on somatic (body) cells.

Reflecting the seriousness of the health effects caused by CMR and the long latent period of cancer, the CMR 1 & 2 cut-off criteria in the Common Position (as well as the additional proposal of the European Parliament to include CMR3 as criteria for toxicity in the case of persistent, bioaccumulating and toxic (PBT) substances and for defining substances as candidates for substitution) represents important additional preventive measures for the general population, as has also been stated for workers in relation to proposals to include CMR category 3 substances within the scope of the worker protection Carcinogens Directive⁶.

2.2 Identification of substances as endocrine disrupters

No specific criteria exist for the classification of pesticides and other chemicals as endocrine disrupting chemicals (EDs). The main reason for this has been the lack of definitive testing protocols for experimental animal studies, and the (frequently) extensive period required to achieve international agreement on such protocols, e.g. at the level of the OECD Test Guideline Programme. Thus, only a handful of substances have been definitively accepted to have such properties on the basis of internationally agreed test guidelines, although many more substances have been postulated to have such effects.

An OECD Task force on Endocrine Disrupter Testing and Assessment (EDTA) has agreed a Conceptual Framework (CF) for the Testing and Assessment of potential endocrine disrupting substances (OECD, 2002). A number of toxicological tests aimed at identifying the endocrine disrupting properties of chemicals are under development, a process that is nearing completion, but it may be some time before a full range of validated testing methods and criteria for identification are developed. Until then, identification of such substances will necessarily be based on a weight of evidence approach.

Some lists of potential EDs have already been drawn up, based on the available evidence for effects in laboratory animals and in wildlife (EC, 2007). Annex II lists some of the active substances on Annex I of Directive 91/414/EEC that are considered potential EDs.

⁶ Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (sixth individual directive within the meaning of Article 16(1) of Directive 89/391/EEC -Codification of Directive 90/394/EEC.

2.3 Identification of substances as presenting a risk of developmental neurotoxic or immunotoxic properties in humans

The impact of including substances “considered to cause a risk of developmental neurotoxic or immunotoxic properties in humans...” is more difficult to assess, and clear, harmonised criteria will be needed to identify such substances, as discussed in Section 4.3. Annex II of this report also lists active substances that could be excluded if developmental neurotoxic or immunotoxic properties are included as cut-off criteria.

As already indicated, in order to achieve the objective of the Regulation, to provide harmonised criteria for the determination of the acceptability or non-acceptability of plant protection substances, criteria will in turn be needed to identify substances (including PPP active substances) that “cause a risk of developmental neurotoxic or immunotoxic effects in humans”. In order to provide transparency in the decision-making process, this may require criteria for classification for such effects under Directive 67/548/EEC or more specifically under the new Regulation on Classification, Labelling and Packaging of Substances and Mixtures, rather than being based on purely risk considerations.

Criteria already exist under Directive 67/548/EEC for classification of substances that present a “Danger of serious damage to health by prolonged exposure” (R48), including substances that cause major functional changes in the central or peripheral nervous systems, including sight, hearing and the sense of smell, assessed by clinical observations or other appropriate methods and substances that produce consistent changes in clinical biochemistry, haematology or urinalysis parameters which indicate severe organ dysfunction.

Similar criteria exist under the new Regulation on Classification, Labelling and Packaging of Substances and Mixtures, for classification of substances for “Specific target organ toxicity” following either single or repeat exposure. Classification of a number of substances having a potential to produce neurotoxicity (e.g. certain organophosphate pesticides) or immunotoxicity (e.g. certain organotin compounds) has therefore already been achieved under current classification criteria, on the basis of data from animal and human studies.

The areas of developmental neurotoxicity and immunotoxicity are however comparatively new areas of public health concern, and while the existence of definitive evidence of such effects would trigger classification, in practice the evidence currently provided by human epidemiological evidence is limited, as described in section 4 below. Such studies are often confounded by mixed exposures to a range of environmental pollutants including pesticides, rather than exposure to a single agent, and do not provide robust data for classification.

Classification for such effects would ideally be underpinned by evidence from toxicological studies in experimental animals. To date, such studies are limited in number. The main reason for this has been the lack of definitive testing protocols for experimental animal studies, and the (frequently) extensive period required to achieve international agreement on such protocols, e.g. at the level of the OECD Test Guideline Programme, as already identified for endocrine disrupters in section 2.2, although considerable progress has been made in this area in recent years. Only a handful of substances have been definitively accepted to have such properties on the basis of internationally agreed test guidelines, although many more substances have been postulated to have such effects.

Although considerable progress has been made in the identification of substances having developmental neurotoxicity and immunotoxicity potential in experimental animal studies in recent years, thus underpinning epidemiological evidence, these data will need to be translated into new classification criteria, or amendment of existing ones, before harmonised classification for these effects can be achieved. Until such time as classification criteria in these areas are agreed, the practical implementation of the European Parliament’s extended criteria to include developmental neurotoxicants and immunotoxicants will have to be implemented on a case by case basis.

However, it should be noted that it has taken decades to gather the human epidemiological data needed to confirm the developmental neurotoxicity of just five substances -- lead, mercury, arsenic, PCBs and toluene. Another 200 industrial chemicals are suspected of causing neurodevelopmental damage during sensitive periods of brain development (Grandjean and Landrigan, 2006) and further advances on our ability to positively identify such substances are urgently needed.

3. Pesticide exposures

People may be exposed to pesticides through their occupation, through domestic use of pesticides in the home, as a bystander to agricultural application of pesticides and through ingestion of residues on foodstuffs. In industrialised countries an increased public awareness of the risks of poisoning from pesticides has led to a decrease in acute episodes of toxicity, with public health concern now focussed on the long-term effects of low-level and chronic pesticide exposure. As such, this study focuses on the adverse effects of long-term exposures, rather than acute poisoning.

It is important to note that individual susceptibility to the negative health effects of pesticides varies, with particular groups of individuals being identified as more vulnerable to these effects. Finally, people's long-term exposure to pesticides involves many different active substances in low doses, as well as exposure to a wide range of industrial chemicals through multiple sources. The cumulative effects of this exposure pattern are not well understood, due to the challenges involved in mapping individual exposure histories. Such mixtures allow synergistic/cocktail effects to develop between compounds and can lead to enhanced toxicity levels.

3.1 Exposure pathways

3.1.1 Occupational exposure

Workers may be exposed to pesticides through a range of occupations, including farming, pesticide manufacturing and packaging, packaging and processing of agricultural products, including forestry products, and gardening. A considerable body of legislation exists at the EU level to protect workers from occupational exposure to dangerous chemicals. Despite this, a large body of case studies and epidemiological studies have identified associations between negative health impacts and exposure to pesticides in the work environment in the European Union. Evidence of associations between occupational exposure and health impacts in the European Union has been found for farmers and agricultural workers⁷, pesticide manufacturers⁸, sawmill operators⁹, and gardeners¹⁰.

In addition, numerous studies investigating pesticide health impacts on children have pointed to parental occupation, in particular farming, as a key exposure pathway¹¹. This suggests that current safety measures have

not been fully implemented or that legislation has not been sufficiently comprehensive to capture and contain all possible exposure pathways, specifically children's exposure. It is important to note that many studies examine past exposure and that safety measures and legislative controls continue to evolve.

Box 2: Pesticide exposures

Exposure to pesticides may be occupational, domestic or through the diet. Workers are potentially exposed to higher levels than the general population, and many of the epidemiological studies reporting adverse health effects relate to occupationally exposed individuals.

Young children may be exposed to pesticides through their diet and parental occupation, in particular farming, may also be a key exposure pathway. They may be particularly vulnerable to potential adverse health impacts due to the fact that their bodies are still developing, and that protective mechanisms such as metabolic pathways are immature. Particular attention should be given to exposure during embryonic/foetal life and/or during childhood as well as possible combination effects.

It has been suggested that combination effects of pesticides may underlie the epidemiological findings of adverse effects in human populations, including young children, but few toxicological studies have been done on mixtures of active ingredients.

⁷ Hoffmann et al., 2008, Eriksson et al., 2008, Merhi et al., 2007, Orsi et al, 2007, Provost et al., 2007, Swaen et al., 2007, Settimi et al., 2003, Sharma-Wagner et al., 2000, Buzio et al., 2002, Dolapsakis et al., 2001.

⁸ Van Maele-Fabry et al., 2008, Becher et al., 1996

⁹ Persson et al., 1993, Persson, 1996

¹⁰ Hansen et al., 2007 and 1992

¹¹ Bassil et al, 2007, Monge et al. 2007, Jurewicz and Hanke, 2006, Feychting et al., 2001, Kristensen et al., 1996, Van Wijngaarden et al., 2003, Fear et al, 1998, Sharpe et al., 1995, Valeri et al., 2002

Indeed, two studies found improving safety recommendations and legislative control to be successful in reducing the occupation health impacts of pesticides for adults (Hansen et al., 2007, Baldi et al., 2006).

3.1.2 Domestic exposure

People may be exposed to pesticides in the home through gardening and pest control products, both for the home and for pets. A number of studies link adverse health impacts amongst children with domestic exposure¹², with particular vulnerability during foetal development¹³.

3.1.3 Dietary exposure

There is a paucity of studies investigating exposure to pesticides through diet. Difficulties arise in making linkages to health impacts through dietary exposure due to the long-term, low dose nature of such exposure, the multiple active substances involved and the challenges of obtaining full information regarding an individual's or population's exposure history. A study comparing the metabolites of pesticides in children on an organic diet with children on a conventional diet found significantly higher levels of metabolites in the urine of the children on a conventional diet, demonstrating that the pesticide residues had passed through the children's system (Curl et al., 2003).

3.1.4 Bystanders

The potential for widespread exposure to agricultural pesticides through drift during application raises concerns about possible health effects on residents, in particular vulnerable groups, living in areas of high agricultural activity. Studies investigating the impacts of pesticides on residents of areas devoted to agriculture have demonstrated that residents suffer adverse health effects in Italy (Fontana et al., 1998), the US (Waterhouse et al., 1996, Carozza et al., 2008), and Spain. The Spanish studies found the presence of very high organochlorine residue levels in human tissue of residents of the Canary Islands, Spain, indicating a chronic exposure to DDT and on-DDT organochlorine pesticides that persists to the present day (Zumbado et al., 2008, Luzado et al., 2006). Unexpectedly, younger subjects (under 18 years) showed residue levels almost twice those of older subjects (65-75 years), suggesting that exposure through environment and consumption is ongoing (Luzado et al., 2006).

3.2 Vulnerable groups

The European Parliament proposals in relation to substances "considered to cause a risk of developmental neurotoxic or immunotoxic properties in humans, taking into account exposure during embryonic/foetal life and/or during childhood as well as likely combination effects" emphasis the importance of additional susceptibility of exposure of the unborn or young child and also of exposure to a combination of pesticides rather than to one single pesticide.

Within the population, there are particular groups of individuals that exhibit enhanced vulnerability to pesticide exposure, meaning that the health impacts of a particular dose are likely to be more serious than for others. This increased vulnerability emerges from the particular physiological condition of those individuals and, in the case of children, from behavioural patterns that increase exposure. This section discusses the particular vulnerability of infants and children, pregnant women, people of ill health on medication, and the elderly.

3.2.1 Infants and children

The vulnerability of the foetus and or young children has been extensively discussed in the literature (see below). This section briefly outlines the physiological and behaviour characteristics of infants and children that increase their vulnerability to pesticides. In the US, these factors led to the 1996 revision of the USA *Federal Fungicide, Insecticides and Rodenticide Act* to include an additional 10-fold safety margin for exposure to pesticide residues in foods (Cohen, 2007, NRDC, 1998).

¹² Rosso et al., 2008, Ma et al., 2002, Buckley et al., 1989, Zahm and Ward, 1998, Davis et al., 1993

¹³ Rudant et al., 2007, Pogoda and Preston-Martin, 1997

A key observation relevant to the discussion of children and pesticide exposure is that 'children are not little adults' (Garry, 2004). Their specific vulnerability to negative health impacts from pesticides stem from the fact that their bodies are still developing, and that the chemical-based signalling systems used to steer development are vulnerable to disruption when exposed to environmental toxicants (Rice and Barone, 2000). The blood brain barrier is not fully developed until an infant reaches six months, leaving the developing brain far less protected than for older children and adults (Rodier, 1995). Due to less developed detoxification pathways, a child's metabolism is less able to metabolise and eliminate toxicants (Ginsberg et al., 2004). In addition, children eat and drink more per kilogram of body weight than adults. Due to their higher metabolic rate and respiratory rate, a specific dose of a pesticide will have a greater impact on a child than on an adult (Bearer, 1995). Finally, children have more years of life ahead of them than adults, giving them more time to develop chronic diseases that take several decades to appear and which may be triggered by early environmental exposure or be determined by continuous exposure (Cohen, 2007).

In terms of increased exposure due to behavioural patterns, children exhibit hands-to-mouth behaviour, have shorter stature, play close to the ground and spend increased time outdoors. Schools located in rural areas often draw their drinking water from small private wells that may be contaminated with pesticide residues (Tamburlini et al., 2002), while children living on farms have been found to exhibit an increased exposure to pesticides in household dust and soil (Simcox et al., 1995). Children often have diets rich in fruit and vegetables, so increasing their exposure to pesticide residues. In addition, the processing undertaken to produce infant foods tends to result in higher concentrations of pesticide residues (Wiles et al., 2008). Nursing infants can ingest pesticide residues through breast milk, where concentration may be amplified through the process of milk production. The neonatal stage is also characterised by a highly permeable gastrointestinal tract, so that toxicants in ingested pesticide residues are more readily absorbed than in the case of adults (Lackmann et al., 2004; Solomon et al., 2002).

Despite the evidence of increased vulnerability of infants and children and the disabling and chronic nature of the resulting health effects, substance-specific data on postnatal developmental toxicity are lacking for many of the currently used pesticides. Cumulatively, the numerous exposure pathways can lead to a high exposure load (NRDC, 1998). Due to the gravity of the potential health impacts, many recommend adopting a precautionary approach to limiting children's' exposure (Jurewicz and Hanke, 2008; Grandjean and Landrigan, 2006).

3.2.2 Pregnant women and fetuses

Cell growth is particularly rapid in the embryo, providing more opportunity for toxicants to cause mutations and congenital anomalies. During early development, the foetus is selectively sensitive to particular toxicants, creating windows of vulnerability (Garry, 2004). The nervous system has a limited capacity to repair any structural damage, if cells in the developing brain are destroyed by chemicals, or if vital connections between nerve cells fail to form during critical periods of vulnerability, there is a high risk that the resulting dysfunction will be permanent and irreversible (Rice and Barone, 2000).

3.3 Cumulative effects

The importance of combination effects of or synergy between pesticides is also well documented in the scientific literature. The vast majority of experimental studies on the safety of pesticides relate to single active substances, as is required under the legislation, yet consumers, including the vulnerable population of young children, are exposed to a mixture of pesticides in the diet. Few toxicological studies have been done on mixtures of active ingredients and there is no generally agreed framework/approach yet for combined risk assessment of pesticides at the European or International level.

However, there are activities ongoing at European and International level concerning approaches to cumulative risk assessment of pesticides which have a common mode of action such as the organophosphates and an amendment to Regulation (EC) No. 396/2005 on maximum residue levels of pesticides in or on food and feed of plant and animal origin emphasises the importance to develop a methodology to take into account cumulative and possible synergistic effects of pesticides to human health.

4. Impacts of pesticides on human health: a general overview

This section provides a general overview of the extensive literature reporting adverse health effects of pesticides in human populations, including occupationally-exposed workers, consumers and in particular the vulnerable population of young children and children born to mothers exposed in pregnancy to high levels of pesticides. The developing embryo and foetus are extraordinarily susceptible to perturbation of the intrauterine environment. Chemical exposures during prenatal and early postnatal life can bring about important effects on gene expression, which may predispose to disease during adolescence and adult life (Grandjean et al, 2007; Grandjean & Weihe, 2008).

The starting point for gathering information for this overview has been the paper prepared for the Ontario College of Family Physicians (Sanborn et al., 2004), which provides a systematic review of the epidemiological evidence for a range of adverse effects reported in the literature associated with exposure to pesticides, including cancer, reproductive outcomes, neurological and mental health effects, genotoxicity (mutagenicity) and immunotoxicity. The results of this review have been updated in this report with the results of key studies reporting such effects since 2004, with an emphasis on European epidemiological studies.

Epidemiology studies on pesticides have found associations with haematological cancer, neurotoxic effects, neurobehavioral disorders, reproductive problems including birth defects and infertility, newborn deaths, etc (Baldi et al. 1998; Faustmann et al, 2000). While toxicological studies in animals on individual active pesticide substances provide clearer evidence of such effects, uncomplicated by confounders such as mixed exposures and environmental and lifestyle factors, no attempt has been made to include such studies in this review, other than in isolated cases.

It should be noted, however, that the human epidemiological data almost always relate to adverse effects on populations considered to be exposed to a mixture of pesticides, although some studies also relate to occupational exposure, again to a mixture of pesticides. Interpretation of the outcome of such studies and the possibility of clearly relating an adverse health effect to one or more pesticides in the environment of the population of concern is fraught with danger. Nevertheless, the publication of Sanborn et al helps to identify many studies that have provided robust evidence for health effects of pesticides in exposed populations.

4.1 Acute poisonings

Pesticides are specifically designed to be toxic to biological organisms, and it has proved difficult to identify specific cellular sites in the target species that are not also found in human tissues. Many pesticides are hence acutely toxic and there are numerous case studies dealing with pesticide poisoning cases, particularly in relation to the organophosphates. These reports relate mainly to exposed workers or accidental poisonings in domestic situations, including in young children.

The World Health Organisation estimates that pesticides poisoning accounts for 300,000 annual deaths worldwide, mostly in low and medium income countries (Goel and Aggarwal 2007). Though an increased awareness of risks from pesticides has led to a decrease in acute episodes of toxicity in industrialised countries, poisonings from agricultural pesticides still occur in industrialised countries. From 1985 through 1990, the U.S. experienced 341 fatalities (28% unintentional) and 25,418 hospitalisations (78% unintentional) due to poisonings with agricultural and horticultural chemicals (Klein-Schwartz and Smith, 1997).

4.2 Cancer

There is a growing body of evidence linking environmental exposure to pesticides with both adult and childhood cancers. Scientific reviews of human epidemiological studies confirm significant positive associations between household or occupational pesticide exposure and various types of cancer, including leukaemia, brain tumours, Wilm's tumour, non-Hodgkin's lymphoma, sarcomas, and prostate cancer (Clapp et al., 2008, Bassil et al., 2007, Infante-Rivard and Weichenthal, 2007, Cohen, 2007, Zahm and Ward, 1998, Littorin et al., 1993).

In particular, children's and pregnant women's exposure to pesticides has been positively associated with cancers both in childhood and later in adult life (Carozza, Li, Wang, Horrel and Cooper, 2008, Bassil et al., 2007). The mechanisms by which pesticides contribute to cancer causation may include producing direct changes to DNA (mutagenic effects), promoting the fixation and proliferation of abnormal clones (including through endocrine effects), and disturbing the body's cancer surveillance mechanisms (immunotoxic effects).

While toxicity generally increases with dosage, mutagenic chemicals and endocrine disruptors may have effects at very low doses, in the absence of a threshold below which no risk exists. Thus even a tiny dose may trigger carcinogenesis (Solomon, 2000). At the same time considerable difficulty exists in proving that a specific substance causes cancer, particularly in a context where people may have been exposed to multiple substances, including non-pesticide agents. Proving the causal link between smoking and cancer took a decade of research, despite the fact that smoking causes more than 90% of all lung cancers (Osann et al., 1993). Based on the understanding that cancer is ultimately caused by multiple interacting factors, scientists and physicians have called for a new cancer prevention paradigm that limits exposure to avoidable environmental and occupational carcinogens (Clapp et al., 2008, Solomon, 2000), and advise specific caution with regard to children's exposure (Garry, 2004, Jurewicz and Hanke, 2006, Bassil et al., 2007).

The sections below summarises the evidence of associations between pesticide exposure

and cancers, focussing on hematopoietic cancers, solid tumour cancers, and childhood cancers. In each case, exposure pathways are discussed and a distinction made between occupational exposure, bystanders or ingestion.

4.2.1 Hematopoietic Cancers in Adults

Hematopoietic cancers affect the blood, bone marrow, and lymph nodes. A 2007 analysis of 13 studies examining the occurrence of hematopoietic cancers in pesticide-related occupations found a significant positive association (Merhi et al., 2007). In addition, bystander exposure has been associated with hematopoietic cancers. Evidence linking pesticide exposure with specific haematological cancers, including non-Hodgkins lymphoma (NHL), leukaemia, and multiple myeloma is summarised below.

The incidence of NHL has been steadily increasing throughout most of the world (Solomon, 2000). A 2004 review of studies investigating the association between pesticide exposure and NHL found that 23 out of 27 studies demonstrated a positive association, many with statistical significance (Sanborn et al., 2004).

Box 3: Cancer

Epidemiological evidence suggests a link between exposure to pesticides and cancer, both in adults (occupationally exposed) and children. Positive associations have been reported between household or occupational pesticide exposure and various types of cancer, including leukaemia, brain tumours, Wilm's tumour, non-Hodgkin's lymphoma, sarcomas, and prostate cancer. In particular, children's and pregnant women's exposure to pesticides has been positively associated with cancers both in childhood and later in adult life.

A number of studies have found the risk of childhood cancers to be higher amongst the children of workers in agriculture and children living on farms, with a particularly strong association for childhood brain tumours.

Considerable difficulty exists however in proving an association between exposure to a specific pesticide and occurrence of cancer, particularly in a context where people may have been exposed to multiple substances, including non-pesticide agents.

Table 1: Significant associations between occupational exposures and NHL

Occupation	Location	Source
Farmers	Italy	Fagioli <i>et al.</i> 1994, Fontana 1998
Farmers	France	Orsi <i>et al.</i> , 2007
Farmers	Canada	Spinelli <i>et al.</i> , 2007
Farmers	USA	Bonner <i>et al.</i> , 2007
Gardeners	Denmark	Hansen <i>et al.</i> , 1992
“Exposed workers”	Sweden	Eriksson <i>et al.</i> , 2008
Sawmill workers	Sweden	Persson <i>et al.</i> , 1993, Persson, 1996
Workers in herbicide manufacturing plant	Germany	Becher <i>et al.</i> 1996

Positive association with NHL have also been proven for bystanders living in areas where pesticides are applied or exposed to drift following application (Solomon, 2000). A positive association was found between the use of phenoxy herbicides and the risk of NHL among residents of the rice-growing areas of northern Italy (Fontana *et al.*, 1998), while a US study demonstrated increased incidence in a Midwestern farming community in the US resulting from sustained bystander exposure to agricultural chemicals (Waterhouse *et al.*, 1996).

The incident rates of both leukaemia and multiple myeloma have also been associated with occupational pesticide exposure. A recent Belgian study provided evidence of the increased risk of leukaemia posed to workers in a plant manufacturing pesticides (Van Maele-Fabry *et al.*, 2008), while a German study investigated the exposure history of 14, 030 leukaemia patients and found that 15% of male and 16% of female patients had been exposed to pesticides at work (Hoffmann *et al.*, 2008). A French study found an increased mortality for male farmers and farm workers from leukaemia (Viel and Richardson, 1993), while a Norwegian study support associations between leukaemia and dairy farming (Kirstensen *et al.*, 1996). Positive associations between occupational pesticide exposure and multiple myeloma were identified in Denmark (Pottern *et al.*, 1992), France (Viel and Richardson, 1993), Italy (Nanni *et al.*, 1998), Norway (Kirstensen *et al.*, 1996) and the Netherlands (Swaen *et al.*, 1992).

4.2.2 Solid Tumours in Adults

Various types of solid tumours in adults have been associated with occupational pesticide exposure. The greatest weight of evidence is available for brain cancer (Sanborn *et al.*, 2004), with positive associations with occupational exposure found in Sweden (Rodvall *et al.*, 1996), Italy (Figa-Talamanca *et al.*, 1993), the US (Samanic *et al.*, 2008, Kross *et al.*, 1996) and France. One French study linked exposure with an excess risk of brain tumours, and especially of gliomas (Provost *et al.*, 2007), while another specifically linked pesticides in vineyards to mortality from brain tumours amongst farmers (Viel *et al.*, 1998).

In addition, occupational exposure has been associated with a heightened incidence of colon cancer in the US (Kang *et al.*, 2008), renal cancer in Italy (Buzio *et al.*, 2002) and the US (Karami *et al.*, 2008, Kang *et al.*, 2008, Hu *et al.*, 2002), cancer of the lip in Norway (Nordby *et al.*, 2007), and cancer of the skin in the Netherlands (Swaen *et al.*, 2007). An increased risk of pancreatic cancer for women agricultural workers was determined in a Spanish study (Alquacil *et al.*, 2000), and for workers exposed to herbicides in a US study (Silverman *et al.*, 2001).

With regards to gender specific cancers, many studies have linked the risk of prostate cancer, the second most commonly diagnosed cancer amongst men worldwide, with occupational exposure to pesticides (Mink *et al.*, 2008). In particular, an elevated risk of prostate cancer has been found amongst farmers in Italy (Settimi *et al.*, 2003), Sweden (Sharma-Wagner *et al.*, 2000, Dich and Wiklund, 1998), and the US (Mills and Yang, 2003, Alavanja *et al.*, 2003).

McGlynn et al. found exposure to persistent organochlorine pesticides (POPs) to be associated with the risk of testicular germ cell tumours, and postulate that exposure during foetal development or via breast feeding may increase risk (Mc Glynn et al., 2008).

A number of female cancers such as breast cancer have also been linked to exposure to pesticides with endocrine disrupting properties, including organochlorines (Kettles et al., 1997). A US study found that exposure to DDT early in life may increase the risk of developing breast cancer (Cohn et al., 2007), while a Spanish study linked the high incidence of and mortality from breast cancer in the Canary Islands, Spain, to ongoing chronic exposure to DDT and its derivatives (Zumbado et al., 2008). A study conducted in Crete, Greece, found that female workers in greenhouses had an elevated risk of incidence for a number of lesions, which are risk markers for subsequent invasive breast cancers (Dolapsakis et al., 2001). Further research is required to assess the combined effects of exposure to multiple agents on the risk of breast cancer (Salehi, Turner et al., 2008). In a study conducted on women in India, Mathur et al. found significantly higher residue levels of organochlorine pesticides in women that had contracted cancers of the reproductive tract, including cervical, uterine, vaginal and ovarian cancers (Mathur et al., 2008). Exposure to pesticides with endocrine disrupting properties has been identified as a risk factor for ovarian cancer warranting further research (Salehi, Dunfield et al., 2008).

4.2.3 Childhood Cancers

In industrial countries, 1 child out of 500 develops a cancer before the age of 15 years, with more than half of those developing cancer before the age of 6 years (Clavel, 2007). Numerous reviews investigating the risk of childhood cancers identify pesticides exposure as an environmental risk factor, most frequently through parental occupational exposure (Ferris et al., 2008, Jurewicz and Hanke, 2006, Clavel, 2007, Infante-Rivard and Weichenthal, 2007, Bassil et al., 2007, Garry, 2004, Tamburlini et al., 2002). In particular, a Norwegian study investigating childhood cancers in farmers' offspring associated the use of pesticides in horticulture with cancers at an early age (Kristensen et al., 1996), while a US study found children living in agricultural areas to have a significantly increased risk for many types of childhood cancers (Carozza, Li, Elgethun and Whitworth, 2008).

The reviews consistently report positive associations between pesticide exposure and increased risk of non-Hodgkin's lymphoma, childhood leukaemia, brain cancer, Wilms' tumour and Ewing's sarcoma. However, uncertainty remains regarding the specific active substances that cause cancer in children. Proving causality is made difficult due to the insufficient number of studies conducted per active substance combined with unavoidable shortcomings in the epidemiological studies. The uncertain risk coupled with the profound impact of childhood cancers lead several authors to advocate a reduction in children's exposure to pesticides (Jurewicz and Hanke, 2006, Bassil et al., 2007).

With regards to hematopoietic cancers, a number of epidemiological studies reported significant associations between parental occupational exposure to pesticides and childhood leukaemia (Monge et al. 2007). Ma et al, found the use of professional pest control services at any time from 1 year before birth to 3 years after to be associated with a significantly increased risk of childhood leukaemia (Ma et al., 2002). A French study found the risk of childhood hematopoietic cancers to be linked to the domestic use of pesticides, in particular maternal use of pesticides during pregnancy (Rudant et al., 2007). A US study found indication of an increased risk for NHL and Burkitt lymphoma in children exposed to agricultural pesticides as bystanders (Carozza, Li, Wang, Horrel and Cooper, 2008).

A number of studies have found the risk of childhood cancers to be higher amongst the children of workers in agriculture and children living on farms, with a particularly strong association for childhood brain tumours. In a study across seven countries, farm- or agricultural-related exposure was positively associated with child brain tumours (Efird et al., 2003). Similarly, a Swedish study found an increased risk of brain tumours in children whose fathers were exposed to pesticides (Feychting et al., 2001), while a US study found paternal use of herbicides or fungicides to be associated with an increased risk of brain tumour among their children (Van Wijngaarden et al., 2003).

Increased risk of childhood brain tumours has also been associated with exposure to pesticides at home (Buckley et al., 1989; Zahm and Ward, 1998; Davis et al., 1993); maternal exposure to various types of flea/tick treatment products for pets during pregnancy (Pogoda and Preston-Martin, 1997), and children's exposure to pesticides used for lawn care in the home both during pregnancy and after birth (Rosso et al., 2008). Evidence has also been found linking parental exposure with Wilms' tumours (Fear et al, 1998, Bassil et al, 2007, Sharpe et al., 1995) and Ewing's sarcoma (Valeri et al., 2002).

4.3 Mutagenicity/genotoxicity

Genotoxic chemicals may have effects at the level of DNA, producing mutations (mutagenesis), or at the level of the chromosome, producing chromosomal aberrations (clastogenesis) or more profound chromosomal effects such as chromosomal deletions (aneugens). Evidence of genotoxicity is of particular interest because of links with possible carcinogenic effects, genotoxic carcinogens being regarded as being potential human carcinogens. Chromosome aberrations have been demonstrated to be a biomarker for cancer risk (Hagmar et al. 1998).

A number of studies have therefore been undertaken in pesticide-exposed subjects and/or their children with the aim of detecting damage to DNA, chromosomes, etc. A 2003 review of the literature concluded that there was a positive association between occupational exposure to complex pesticide mixtures and the presence of chromosomal aberrations (CA), sister-chromatid exchanges (SCE) and micronuclei (MN) in the cells of occupationally-exposed subjects, although negative results were found in other studies (Bolognesi, 2003). Sanborn and co-workers reviewed 22 robust cytogenetic studies of pesticide-exposed subjects and reported a statistically significant increase in frequency of chromosome aberrations (CAs) in 50% of these studies (Sanborn et al. 2004). Although it has proved difficult to link such effects to specific pesticides, and the effects of confounders such as smoking and other environmental pollutants must be taken into consideration (Sanborn et al. 2004), genotoxic effects have been reported on the spermatozoa of carbaryl-exposed workers (Xia et al, 2005) and a high incidence of fetal DNA fragmentation has been demonstrated recently in children born to mothers living in a farming community in southern Sri Lanka and exposed to organophosphate pesticides during the pesticide spraying season (Samarawickrema et al. 2008).

4.4 Reproductive dysfunction

4.4.1 General

As reported in particular by Sanborn and co-workers and other Canadian researchers, an association between pesticide exposure and a range of adverse reproductive outcomes has been reported in a number of papers in the literature, including gynaecological and endocrine dysfunction in women with recurrent pregnancy loss and altered placental characteristics (e.g. Sanborn et al., 2004; 2007; Weselak et al, 2007; Wigle et al, 2008). Reproductive effects have been reported in both human and animal studies for a large number of pesticides, particularly developmental effects. Thus occupational exposure to pesticides and reproductive hazards for workers, their spouses, as well as developmental effects on their children have become a major public health issue. Positive epidemiological evidence is considered to exist for persistent organic pollutants such as DDT and DDE, dioxins and furans, polychlorinated and polybrominated biphenyls and methyl mercury, some of which have been used as pesticides in the past. However the epidemiological evidence for other pesticides including those still in common use is less convincing, in part because of mixed exposures and other confounders. The issue of endocrine dysfunction and the possible links with adverse effects on reproductive capacity is discussed in section 4.4.2 below.

Common reproductive outcomes of known and unknown etiology include changes in sexual behaviour, infertility, pregnancy outcomes, and functional change, reported in animal studies with pesticides such as aldrin, atrazine, benomyl, captan, carbaryl, dieldrin, dinoseb, ioxynil, lindane, maneb and paraquat (London Food Commission, 1988.). Developmental (teratogenic) effects have been reported with aldrin, benomyl, captan, captafol, 2,4,5-T, dichlorvos and diazinon (Robbins, 1991, London Food Commission, 1988).

In humans a number of studies have linked pesticide exposure, both maternal and paternal, with adverse pregnancy outcomes such as miscarriage, preterm birth, SGA, stillbirth, neonatal death, low birth weight and length, foetal distress, and sex ratio (e.g. Crisostomo & Molina, 2002; Dimich-Ward et al., 1996; Hourani & Hilton, 2000; Perera et al. 2003; Jarrell et al., 1998, 2002; Savitz et al, 1997; McGready et al. 2001; Kumar, 2004; Idrovo & Sanín (2007).). Effects have also been reported on child development after in utero exposures (developmental delay, death, retarded growth parameters including reduced weight, height, and head and arm circumference) (McGready et al. 2001; Berkowitz et al, 2004; Windham & Fenster, 2008; Wolff et al. 2007). Specifically in the case of exposure to organophosphate pesticides, effects on foetal growth and development, blood cholinesterase activity and placental charac-

Box 4: Reproductive dysfunction

Occupational exposure to pesticides has been associated with birth defects, fecundability, foetal death and intrauterine growth retardation. Other adverse reproductive outcomes include gynaecological and endocrine dysfunction in women with recurrent pregnancy loss and altered placental characteristics.

Reproductive effects have been reported in animal studies for a number of pesticides, particularly developmental effects. Positive evidence of reproductive effects exists for persistent organic pollutants such as DDT and DDE, dioxins and furans, polychlorinated and polybrominated biphenyls and methylmercury, some of which have been used as pesticides in the past. The evidence for other pesticides including those still in common use is less convincing, in part because of mixed exposures and other confounders.

teristics have been described (Levario-Carrillo et al, 2001; Wolff et al. 2007; Peiris-John & Wickremasinghe, 2008).

Various malformations have been reported to occur in the children of parents exposed to high levels of pesticides, including hydrocephaly, vascular malformations (Loffredo et al., 2001), congenital long bone and limb defects (Engel et al. 2000) and anophthalmia, as well as considerably higher miscarriage and stillbirth rates (Rita et al, 1986; Arbuckle et al., 1999, 2001). Retrospective studies found a high rate of stillbirths and a significant increase in congenital malformations of the neural tube and the palate in children born to Vietnamese civilians in a period coinciding with two years of heavy spraying of pesticides (Kunstadner, 1982; Kunstadner et al. 2001).

Sanborn and colleagues concluded on the basis of their review that occupational exposure to agricultural chemicals may be associated with adverse reproductive effects including: birth defects, fecundability, foetal death and intrauterine growth retardation (Sanborn et al., 2004).

4.4.2 Endocrine disruption

There is convincing evidence that a number of pesticides and other environmental chemicals, notably persistent organic pollutants such as DDT, DDE and the polychlorinated and polybrominated biphenyls can affect endocrine function in laboratory experiments and in wildlife (Vos et al. 2000; Rogan & Ragan, 2007; Hotchkiss et al. 2008). Such chemicals are termed Endocrine Disrupting Chemicals (EDCs), and considerable efforts have been made over the last decade to identify such chemicals using internationally agreed test guidelines. Lists of potential EDCs have been drawn up, based on the available evidence for effects in laboratory animals and in wildlife (EC 2007). Although there is extensive low-level human exposure to many of these chemicals via the environment, it has been difficult to demonstrate similar effects on human endocrine function from such exposures, in part because of confounders such as mixed exposure to several potential EDCs and other environmental factors. Nonetheless, there is no reason to believe that the effects that have been manifest in ecosystems do not also occur in exposed human populations (Rogan & Ragan, 2007).

Endocrine disruption has been explored as a cause for a number of the adverse reproductive outcomes summarised earlier, including gynaecological dysfunction in women with recurrent pregnancy loss (Sanborn et al., 2004; 2007; Weselak et al, 2007; Wigle et al, 2008) and also in the increasing trend towards early puberty in girls (Hotchkiss et al. 2008). In addition, pathways and targets for endocrine disruption extend beyond the traditional estrogen/ androgen/ thyroid receptor-mediated reproductive and developmental systems, effects on which may be manifest as reproductive disorders both in the parental generation and in the offspring

Box 5: Endocrine disruption

Emerging evidence suggests that certain chemicals including pesticides can interact with the endocrine systems of living organisms, including those of humans, resulting in altered function and consequential adverse health effects, particularly on reproductive capacity. Endocrine disruption has been explored as a cause for a number of the adverse reproductive outcomes summarised earlier, including gynaecological dysfunction in women with recurrent pregnancy loss and also in the increasing trend towards early puberty in girls.

(Hotchkiss et al. 2008). Thus, more recently it has been suggested that EDCs may play a role in obesity and type II diabetes in the United States and other populations (Newbold, 2008).

4.5 Neurotoxicity, neurobehavioural and cognitive effects

Several classes of pesticides, including the organophosphate compounds first developed for military use as “nerve gases”, have long been known to have acute neurotoxic effects on humans. In recent years a number of links between chronic, low-dose exposures and long term neurological problems have been identified. Sanborn mentions “a remarkable consistency of findings of nervous system effects of pesticide exposures from pathophysiological and functional tests, through clinical examinations, to health care use and mortality data” (Sanborn et al., 2004, p. 88).

Types of neurotoxic effects linked to pesticide exposure include: (1) neurodegenerative diseases, such as Parkinsons and Alzheimer’s; (2) functional nervous system impacts, including cognitive problems; (3) mental and emotional impact; and (4) developmental neurotoxicity, i.e., impacts on foetuses and young children caused by low-dose exposure to certain chemicals, including some pesticides, during critical moments of brain development.

While convincing experimental evidence in animals exists to document the developmental toxicity of many pesticides, epidemiological evidence from human populations is weak (Andersen et al., 2000). The lack of field-based evidence is due to the difficulties in proving associations between exposure to single substances over long time periods in the large population groups required to generate robust data, particularly when other parameters such as nutrition and exposure to other industrial chemicals are impossible to control. The most consistent associations found are between previous pesticide poisonings, particularly from organophosphates and carbamates, and deteriorations in current functions. It is more difficult to distinguish between chronic or cumulative exposure and current exposures, except where organophosphates were under scrutiny and cholinesterase levels could be measured, since in many populations, exposures are a combination of past poisonings, cumulative exposure and current work and home exposures.

The majority of the approximately 200 industrial chemicals (including 90 pesticides) that have caused clinical intoxications also cause effects on the nervous system (Kimbrough et al., 1989; Grandjean et al., 1991). However, neurotoxicity testing is not part of the current requirements for classification of new chemicals, except for organophosphate pesticides. Subtle forms of neurotoxicity are difficult to examine in experimental models, and the extrapolation to humans is complicated. Thus the total number of industrial chemicals with a neurotoxic effect could be much higher than those for which detailed human evidence is available.

4.5.1. Neurodegenerative diseases

A number of epidemiological studies have found a strong link between pesticides exposure and Parkinson's disease, a neurodegenerative disease characterized by progressive tremor, bradykinesia (slowness in the execution of a movement), rigidity, and postural instability (Brown et al., 2006; Hancock et al., 2008). Methodological weaknesses in some studies made it impossible to conclude a causal relationship with any particular pesticide compound(s). However, a case-control study that investigated associations between several environmental factors and PD in five European countries-- Scotland, Italy, Sweden, Romania and Malta -- did find that the significantly increased odds ratios for Parkinson's disease/parkinsonism with an exposure-response relationship for pesticides suggested a causative role for pesticides, with repeated traumatic loss of consciousness also associated with increased risk (Dick, 2007). Another study in southwestern France found an association between occupational pesticide exposure and Parkinson's disease in the elderly (Baldi et al. 2003). Similarly, a Danish cohort study found a high risk of Parkinson's disease for men and women in agriculture and horticulture (Tüchsen and Jensen, 2000).

Links between pesticide exposure and Alzheimer's have also been investigated, but the findings are more inconclusive. A Spanish study that looked for epidemiological evidence of an association between Alzheimer's and the most frequently studied occupational exposures found an increased and statistically significant associations with pesticide exposure, while evidence of association with the remaining occupational agents was inconclusive (solvents, electromagnetic fields) or absent (lead, aluminium) (Santibáñez et al., 2007). On the other hand, a case control study in Quebec that assessed environmental pesticide exposure based on residential histories and agricultural records for herbicide and insecticide spraying failed to show a significant risk of AD with exposure to pesticides (Gautier, et al., 2001).

4.5.2 Functional nervous system impacts, such as cognitive problems

A 2003 review of the literature on neurobehavioral toxicity of pesticides (Colosio et al., 2003) found associations between exposure to DDT and fumigants with permanent decline in neurobehavioral functioning and increase in psychiatric symptoms, but could not draw firm conclusions due to the limited number of studies available and lack of knowledge on exposure levels. Impairments in neurobehavioral performance and, in some cases, emotional status were long-term consequences of acute poisonings but these effects could have been expressions of damage and not of direct neurotoxicity. Slight changes were however consistently observed in sheep dippers, suggesting an association with occupational exposures at relatively higher exposure levels. A study looking at neurobehavioral performance in preschool children from agricultural (AG) and non-agricultural (non-AG) communities in the USA found that the AG children – at high risk of exposure to pesticides because of the close proximity of their homes to fields where pesticides are applied and from take-home exposure --performed poorer on measures of response speed and latency compared to non-AG children (Rohlman et al., 2005).

A study of Bordeaux vineyard workers, most of whom had used fungicides, found a possible association between reduced neuropsychological performances and long-term exposure to pesticides (Baldi et al., 2001). These findings were confirmed in a prospective cohort study of French elderly which found lower cognitive performance in men who had been occupationally exposed to pesticides, as well as higher risks of developing Parkinson's disease and Alzheimer's disease (Baldi et al., 2003).

4.5.3 Mental and emotional impacts

Some epidemiological studies have found associations between levels of exposure to pesticides and mental and emotional symptoms (Keifer et al., 1996; van Wijngaarden, 2003). A study of Canadian farmers found an association between pesticide use and suicide (Pickett et al., 1998), while a cross-sectional survey of workers in south-eastern Spain looked at exposure to a combination of pesticides, including cholinesterase inhibitors such as carbamates and organophosphates (OPs), in intensive greenhouse agriculture (Roldán-Tapia et al., 2008). After controlling for confounds (age and educational level), the findings showed association of long-term exposure and worse performance in neuropsychological functions, which was interpreted as evidence of a chronic effect of cumulative high exposure to OPs and carbamates.

4.5.4 Developmental neurotoxicity

One out of every six children in the U.S. is estimated to have a developmental disorder, and most of these are nervous system disabilities, such as autism, attention deficit disorder, mental retardation and cerebral palsy (Boyle CA et al., 1994). These disorders are difficult to treat and may be permanent, therefore costly to the families and societal structures that must care for these children and the adults they may become.

The causes of such neurodevelopmental disorders are mostly unknown. However, as mentioned already in section 3.2.3, during foetal development and through early childhood the developing brain is particularly susceptible to the adverse effects of neurotoxicants, due to its immaturity and ongoing development (Rodier, 1995; Andersen et al., 2000). Optimal brain development requires that a multitude of processes must take place in a tightly controlled sequence, with specific substances used to trigger each step of the processes. Neurotoxicants can interact with these substances to disturb the signalling process in a way that can halt or inhibit a development process. Consequences for the developing child can be substantial and include permanent abnormalities, such as brain damage, behavioural disorders and reduced intelligence (Tamburlini et al., 2002).

The first evidence of a substance's neurotoxicity has usually been found in adults with occupational exposure. Epidemiological evidence of neurobehavioural deficits in children with prenatal exposures at levels not toxic to adults may not emerge until decades later. Today several hundred industrial chemicals, including at least 90 pesticide substances, have come to be recognised as neurotoxic to adults and are also suspected of causing subclinical brain dysfunction (Grandjean and Landrigan, 2006). Because exposure to these chemicals during foetal development can cause brain injury at levels much lower than levels affecting adult brain function, and because of the gap in time between identification of neurotoxicity to adults and the gathering of epidemiological data on effects on children, Grandjean and Landrigan (2006) speak of a "silent pandemic" of neurodevelopmental disorders caused by industrial chemicals.

Studies of pre-school children in pervasive exposure situations (e.g., farm worker families) have had to consider maternal, in-utero and early childhood exposures. Studies of children diagnosed with autism spectrum disorders (ASDs) in the California Central Valley found a strong link between mother's residential distance from sites of agricultural pesticide application and the stage of gestation at the time of pesticide use (McGovern, 2007; Roberts et al., 2007). Three time windows were of special interest: the period leading up to and covering central nervous system embryogenesis (1 week before conception through 7 weeks after), the period leading up to and covering neural tube development (4 days before conception through 24 days after) and overall gestation (2 weeks before conception through birth). The association pointed to a connection between organochlorines and ASDs but could not conclude causality. However, ASD risk increased with the poundage of organochlorine applied and decreased with distance from field sites.

4.6 Immunotoxic effects

There is evidence that some pesticides are immunotoxic in experimental animal studies, and a growing body of epidemiological studies document pesticide-related effects in the immune systems of humans. Current science cannot yet accurately characterize the public health implications from pesticide-associated immune system damage at the population level or for specific groups. However the evidence to date clearly indicates that exposure to certain pesticides, individually and/or in combination with other xenobiotics, does compromise immune system function, and may pose potentially significant threats to human health (Duramad et al 2007, Sanborn et al 2004, Galloway and Handy 2003, Phillips 2000, Solomon 2000, Voccia et al 1999, Banerjee et al 1996, Faustini et al 1996, Reppetto and Baliga 1997).

Pesticide-associated immune system effects documented in humans include hypersensitivity reactions (which can range from dermatitis to asthma or anaphylaxis); suppression or stimulation of immune system function (in some cases by the same pesticide at different doses) and cancers of the immune cell lines (Sanborn 2004, Solomon 2000, Voccia et al 1999). Effects on the immune system may be manifest as altered susceptibility to infectious and other disease states including cancer.

Pesticides found to date to have some degree of immunotoxic effects include organotin compounds; some fungicides; phenoxy and triazine herbicides, and insecticides in the organophosphate, carbamate, organochlorine and pyrethroid classes (Sanborn et al 2004, Wilson 2004, Galloway and Handy 2003, Colosio et al 1998, Faustini et al 1996).

Recent studies documenting immune system impacts in people exposed to pesticides in the EU include altered immune profiles in Italian agricultural workers exposed to the EDBC fungicide mancozeb and the herbicide propanil (Corsini et al 2005, 2007); impaired humoral and cellular immune responses in Germans exposed to the organochlorine wood preservative pentachlorophenol (Daniel et al 2001); and reductions of the percentage of immune cells that identify and destroy virally infected cells in Italian farmers exposed to 2,4-D and phenoxy herbicides 2,4-D and MCPA, a condition that may increase the risk of certain cancers, e.g. lymphomas (De Roos et al 2003, Faustini et al 1996, Newcombe 1992).

In addition to direct immunotoxic impacts, some pesticides may be indirectly immunotoxic. For example, xenobiotic-induced dysfunction in the neuroendocrine system can have immune effects, not through direct action on immune cells, but by disrupting brain-immune interactions (Fuchs 1994). Organophosphate pesticides may also cause indirect immunotoxic effects as a result of changes they induce in the nervous system (Galloway and Handy 2003)

Immunotoxicology is a relatively new field, and many studies emphasize a pressing need for more appropriate testing protocols and screening methods in order to identify pesticide immune effects of prognostic significance. As in the case of developmental neurotoxicity, intrinsic differences between and within individuals make the immunotoxic effects of occupational and environmental pesticide exposure difficult to study (Solomon 2000) Thus, where they exist, current regulatory standards relating to immunotoxicity are unlikely to be adequately health protective, particularly for occupationally exposed and vulnerable groups including foetuses, infants and children.

Because science in this area is evolving rapidly, increasing knowledge of pesticide effects on the immune system can be expected to influence regulatory decision making for some time to come. Under these circumstances inclusion of immunotoxic parameters within the regulation, as proposed in the EP version, seems justified as a public health measure.

5. Potential benefits from implementing the cut-off criteria

The previous section summarizes the findings from various epidemiology studies that have found strong associations between exposure to pesticides and various health end-points. Because some of the health impacts, including several cancers and Parkinson's disease, may not develop until years after exposure, such studies may not be able to identify clear associations until considerable time has elapsed.

As already noted, humans are exposed to pesticides through a number of pathways, including occupational exposure, the consumption of food containing pesticide residues, inhaling, ingesting or adsorbing pesticides through the skin as a bystander to application, and through drinking water contaminated with pesticides. The long-time periods over which exposure can take place, variations in individual vulnerability and the synergistic effects of exposure to multiple substances in the everyday environment make analysis of the human health impacts of individual substances extremely complex. Proving a causal association between a specific substance and long-term illness such as a neurological or immunological disorder is particularly challenging.

The lack of precise and corroborated data on the health effects of exposure to many active substances generates some uncertainty regarding the benefits of limiting their access to the market. For all of the above reasons, estimation of the avoided deaths and other health benefits that may be achieved through controls over specific pesticides is an uncertain practice at the present time.

In this section we summarize some of the key studies to date in this area. We then apply a few of the methodologies to arrive at initial estimates of (1) the potential scale of human health impacts from pesticides, and (2) costs that could be avoided by eliminating exposures to specific substances caught by the proposed cut-off criteria. Because of the uncertainties identified above, any results – including those of our own efforts -- should be considered indicative rather than definitive

5.1 Previous efforts to estimate costs to human health from exposure to pesticides

Most of the potential health benefits from restricting the use of certain pesticides would accrue through avoiding the costs of health impacts associated with pesticide exposure. These costs could include health service costs, the value of an individual's lost quality of life, the value of a statistical life lost due to a pesticide-related death, or loss of productivity (days of work lost) due to a pesticide-related poisoning, whether acute or chronic.

The difficulty of estimating these benefits in relation to reduced exposure to chemicals is commented on by virtually every study that has attempted such an assessment (Bowles and Webster, 1995). Most studies have limited their efforts in this area to measuring direct costs linked to acute poisonings caused by exposure to specific chemicals. Very few studies have taken on the challenge of estimating economic benefits in terms of reduced costs from chronic health effects linked to specific chemicals, because of the difficulty in showing causation due to exposure.

Several global estimates have been ventured in this area. A World Bank study (Lvovsky et al., 2001) estimated that in established market economies pollution from agro-industrial chemicals and chemical pollution from diffuse sources caused between 0.6% and 2.5% of the total burden of disease (that is, deaths and general ill health) with a central estimate of 1.5%. These estimates were based on conservative (5%) and liberal (20%) percentages of the total burden of disease attributable to pesticide exposure in some 15 disease categories. The degree of imprecision in these assumptions indicates the lack of a robust understanding of the full impact of chemicals on the general health of the population.

A frequently cited study on the environmental and economic costs of pesticide use in the U.S. (Pimentel, 1992) estimated annual U.S. costs of human health effects due to pesticide exposures at \$787 million (approximately €55 million at current values). Estimates of costs attributable to acute poisonings included hospitalisations (\$6.8 million), outpatient treatment (\$17 million), and lost work due to poisonings (\$1.76 million). The figures for persons hospitalised (est. 2380 persons/year x 2.84 days) and for lost days of work due to poisonings (est. 4680 workers x 4.7 days) were based on two national studies of hospitalized pesticide poisonings, carried out through USEPA (Keefe et al. 1990; as quoted by Pimentel 1992). The study also calculated that the 27 fatalities from pesticide poisoning that occurred during the selected year cost \$2 million each, or \$54 million total.

More controversially, the Pimentel study also tried to estimate costs of health impacts and environmental damage from chronic exposures to pesticides. For example, on the basis of an assumption that 1% of all cancers could be attributed to pesticide exposure, it arrived at an annual cost of treating pesticide-induced cancers of \$707 million. However, this methodological approach has been criticised as highly speculative.

A 2001 study by Pretty et al. that assessed the external costs of UK agriculture declined to estimate costs of chronic exposure to pesticides because of the difficulties in establishing a reliable causal link between pesticide exposure and a particular health outcome. That study's estimates of health costs to humans counted only the costs of acute poisonings on the basis of figures for hospitalisations and days of work lost specifically linked to high-level pesticide exposure, to arrive at an annual cost of \$2 million. This approach was also taken by Waibel et al. in a 1999 study focusing on Germany, which estimated a total of \$14 million in annual health costs in that country due to acute pesticide poisonings.

Several innovative studies of the benefits of reduced exposure to chemicals have been carried out in relation to REACH (see Annex III for more detailed descriptions). The European Commission's Extended Impact Assessment estimated that the total health benefits from REACH would be some €50 billion over the next 30 years, assuming 4,500 lives saved every year due to REACH and using the value of €1 million per statistical life (Commission Staff Working Paper, 2003). Another study estimated occupational health impact reductions within the EU-15 arising from REACH would range from some €18 billion to €27 billion over a 30 year period, with more than 99% of the reductions coming from the avoidance of future cancer deaths (RPA, 2003).

A study for the European Trade Union Technical Bureau for Health and Safety (Musu, 2004) calculated that at least 4% of occupational cancer cases and 2% of occupational neurological disease cases were related to chemical exposure. Finally, a Sheffield University study analysing the impact of REACH on the health of the EU-24 work force assumed that all cases of occupational skin and respiratory diseases were likely to be affected by REACH, and estimated cost savings due to REACH at around €3.5 billion over the next 10-year period and an aggregate cost savings of €90 billion over a 30-year time period, after which the full effects of REACH would be in place.

A 2007 study on the burden of occupational cancer in Great Britain (Ruston & Hutchings) aimed to produce an updated estimate of the current effects of occupation on cancer mortality. The primary measure of the occupational burden of cancer was the attributable fraction (AF), i.e., the proportion of cases that would not have occurred in the absence of the occupational exposure. The study calculated occupation-attributable burdens for six types of cancers, using statistically significant risk ratios (RR) or odds ratios (OR) derived from human epidemiology studies. The methodology considered the number of people exposed as a fraction of the total labour force, and then on the basis of a formula derived the attributable fraction (AF) of a disease within a particular occupation. The study concluded that the current burden of six cancers due to past occupational exposures is 8% for men and 1.5% for women. It considered this to be a conservative estimate given that large numbers of workers, including farmers and other agricultural workers, were exposed to several carcinogenic agents over the risk exposure periods.

5.2 Potential health benefits from exclusion of CMR 1-2 & endocrine disruptors

To attempt to identify the scale of the potential cost savings from the cut-off criteria, the following methodology was used. Firstly, studies on the health benefits of chemical legislation were reviewed, including the assumptions used to calculate these benefits. Most of these related to the REACH Regulation, and summaries can be found in Annex III. Then the assumptions made in the various studies on the benefits of chemicals legislation were used (extrapolated) to estimate the potential cost savings that may be achievable through implementation of the proposed cut-off criteria.

For example, use of the figures in the 1992 study by Pimentel et al. (when the U.S. population was 256 million) for the incidence of poisonings, if extrapolated to the EU population of 490 million at the present time, derives an estimated number of hospitalisations due to pesticide poisonings of 8958 persons/year, as well as an estimated lost days of 19,000 work per year due to poisonings. Using the 1992 U.S. figures for costs of hospitalisation and lost days of work, European costs could reach €9.7 million per year for hospitalisations, and €2.5 million for lost work due to poisonings. Since these costs are based on 1992 cost information, these estimated costs must be considered very conservative.

Another extrapolation can be made from the 1992 Pimentel assumption that less than 1% of US cancer cases are due to pesticides. In 1995 there were an estimated 2.6 million new cases of cancer in Europe, representing over one-quarter of the world burden of cancer. In 2002 worldwide, an estimated 11 million cancer cases were diagnosed; one quarter or 2.75 million being in Europe. A later study estimated 3 million new cases and 1.7 million deaths each year in Europe from cancer (Ferlay et al 2007). All these estimates are similar -- between 2.6 and 3 million cases of cancer a year in Europe. Using the lower bound figure of 2.6 million and assuming less than 1% were due to pesticides, this equates to less than 26,000 cases of cancer per year that are due to pesticides. Using the standard value per statistical life (VOSL) of €1 million, this equates to a maximum possible saving of €26 billion each year.

It is not clear how many cases of cancer would be avoided by the strict cut-off criteria in the Common Position. However, it could be assumed that if the remaining active substances meeting the criteria for classification as carcinogenic categories 1 and 2 were restricted, a significant proportion of the maximum €26 billion could be saved. In addition, further savings could be possible in the future, if some substances now classified as CMR3 are reclassified as CMR 2 on the basis of new scientific evidence.

A new study by RPA (July 2008) carried out for the UK Pesticides Safety Directorate extends the methodology used by Rushton (see above) to consider the benefits of pesticide regulation. It developed four different case studies, two of which focused on the potential occupational health benefits arising from withdrawal of approvals for specific active substances. For the estimates of occupational health benefits, the RPA study adapts this approach to develop estimates of the farm labour force exposed to a specific pesticide during the relevant exposure period, using UK-specific data. The study then used statistically sound risk ratios or odds ratios for seven different pesticides. However, the July 2008 study by RPA takes on this challenge.

The RPA study estimated the benefits of withdrawal of approvals for the seven active substances at a lower range of £93 to £186 million in potential cancer cases avoided for spray operators only, with an upper range of £354 to £709 million in potential cancer cases avoided for the maximum exposed farm worker population in the UK, over the relevant exposure period of 30 years (RPA, 2008). These figures are for the UK only. If expressed in Euros and extrapolated to the EU population as a whole (which is roughly 8 times the size of the UK), the benefits of withdrawing approvals for those substances could have an upper bound range of €3,568 to €7,160 billion over the coming 30 years for the maximum exposed farm worker population.

5.3 Potential health benefits from exclusion of developmental neurotoxic and immunotoxic active substances

A number of estimates have been made for the overall costs to society of developmental neurotoxic disabilities such as autism and loss of cognitive ability. This section reviews a few of these studies and considers the possible scope of such impacts on an EU-wide basis.

Costs of autism. A 2006 U.S. study estimated that it can cost \$3.2 million to take care of an autistic person over his or her lifetime, and that the annual cost of caring for all people with autism in the US comes to an estimated \$35 billion per year (Ganz, 2006). Two cost components were considered: direct costs (medical costs including physician and outpatient services, prescription medication, behavioural therapies and non-medical including special education and child care) and indirect costs (lost productivity both for the person with autism and for the person's parents).

By way of comparison, a recent study on the *Economic Consequences of Autism in the UK* estimated that 107,000 UK children and 433,000 adults have an autistic disorder. The overall cost of caring for the U.K.'s children with autism was estimated at £2.7 billion a year, while the cost of carrying for its autistic adults was estimated at £25 billion – an annual cost to the UK of just under £28 billion. The lifetime cost to society for someone with autism was estimated to be as much as £4.7 million per person.

A Swedish study arrived at annual costs per child of a similar magnitude to those in the UK study (which work out to approximately €32,000/year per child). The Swedish study estimated the societal economic consequences of autistic spectrum disorder at approximately \$50,000 per child (Järbrink, K., 2007). In addition, parents of ASD-diagnosed children spent an average of some additional 1000 hours a year to care and support their child, which placed a significant burden on families in addition to out-of-pocket expenditures.

The potential impacts of exposure of children to developmental neurotoxic pesticides could be similar to the now well-documented impacts of exposure to lead and mercury. One study estimated the annual cost to the U.S. of lead poisoning as \$43.4 billion (Landrigan et al. 2002). A later analysis focusing on the neurodevelopmental impacts of methyl mercury --specifically loss of intelligence in children used national blood mercury prevalence data to estimate that between 316,588 and 637,233 infants born each year in the U.S. had cord blood mercury levels over levels associated with loss of IQ (Trasande et al., 2005). The study estimated the cost of the resulting loss of intelligence in terms of the diminished economic productivity that would persist over the lifetime of these children, which was considered to come to some \$8.7 billion annually (range, \$2.2-43.8 billion, in 2000 US\$).

5.4 Areas for further analysis

As flagged above, few studies have ventured to estimate the health-related costs of certain chronic health end-points that might be attributable to exposure to a specific chemical. As mentioned earlier, the July 2008 study by RPA took on this challenge, using UK-specific data. In the course of carrying out this impact assessment, efforts were made to apply the RPA methodology to a specific chemical (chlorpyrifos) to the EU agricultural labour force, using Eurostat data. This effort did not prove successful due to lack of data, e.g., amounts of chlorpyrifos used in certain crops across the EU that could be used to estimate exposure. In addition, the inherent uncertainties in the use of risk-ratios and odds-ratios which reflect associations between exposure and cancer outcomes, rather than demonstrated causality, need to be recognised. Nonetheless, if the necessary data could be developed the methodology could provide some concrete cost figures to indicate benefits that might be achieved by reducing occupational exposure to specific active substances, in terms of particular health end-points.

There is now an extensive body of scientific work that has found statistically sound evidence of strong associations between exposures to pesticides as a group and to specific substances. What are missing are robust economic analyses of the true costs of chronic exposures to chemicals in general and pesticides in particular, similar to the studies calculating the various benefits that were expected to accrue due to REACH.

6 Conclusions

This study has compiled an overview of recent epidemiology studies that have found strong associations between pesticide exposure and a range of health impacts. It has also endeavoured to assess some of the health benefits that may be expected in the years to come if exposure to certain chemicals is eliminated, thereby saving society the costs that would be expected from their associated impacts on human health. The following conclusions were reached:

6.1 Hazard-based cut-off criteria are justified where a preventive approach is needed

It should be recognised that the current risk-management system under Directive 91/414/EEC for evaluating active substances has already succeeded in eliminating a number of substances because they were considered to pose unacceptable risks to human health and/or the environment. As a result of the more than 15-year-long review process under Directive 91/414/EEC, many of the most problematic active substances have now been withdrawn from the EU market, or not approved for Annex I inclusion. Some of the not-approved substances had been in use within Europe for several decades – long enough for epidemiological evidence to accumulate about associations between specific chemicals and health impacts among exposed populations.

In the course of the literature review carried out for this study, substance-specific epidemiology studies were not available for the majority of the substances that would be caught by the cut-off criteria of CMR 1 & 2, endocrine disruption, etc. However, as already pointed out, the absence of evidence of effects does not equate to absence of effects. The long latency periods between low-level exposures and emergence of firm evidence of health impacts means that it can take many years for such evidence to accumulate.

Although only a few of the epidemiology studies reviewed in the course of preparing this study have been able to link specific chemicals with specific health impacts, the body of scientific work in this area indicates a need for a preventive approach that focuses on reducing human exposure to certain pesticides to a minimum. In the absence of epidemiology studies, hazard-based criteria derived from experimental and animal-based studies are important tools for prevention and should be considered for those substances where negligibility of exposure cannot be assured.

6.2 The proposed cut-off criteria reflect the seriousness of associated health effects

The CMR 1 & 2 cut-off criteria in the Common Position and in the European Parliament's first reading amendments reflect the seriousness of the health effects caused by substances that are carcinogenic, mutagenic and/or toxic to reproduction. Given that many CMR3 substances may be reclassified at a future point as CMR2, the additional proposal of the European Parliament to include CMR3 as criteria for toxicity in the case of persistent, bioaccumulating and toxic (PBT) substances and for defining substances as candidates for substitution also deserves strong consideration.

The cut-off criterion for endocrine disruption addresses the increasingly strong emerging evidence that certain chemicals can interact with the endocrine systems of living organisms, including those of humans, resulting in altered function and consequential adverse health effects, particularly on reproductive capacity.

The active substances that would be eliminated by the cut-off criteria are of high concern even if, in a number of cases, there is not yet epidemiological evidence to back up the laboratory and animal studies that have started to flag problems. In such cases of scientific uncertainty, where inaction could have serious consequences, additional policy measures may be warranted in order to ensure sufficient health protection for EU citizens.

6.3 The special vulnerability of children argues for extreme caution with respect to developmental neurotoxicants

This study found a wide range of evidence pointing to a strong association between neurological problems in children and exposure to pesticides during critical periods of brain development. Due to the gravity of the potential health impacts and the high costs to society from low-level chronic damage to children from neurotoxicants, many experts have recommended adopting a precautionary approach to limiting children's exposure.

Several studies noted that it took decades to gather sufficient epidemiological evidence of the neurotoxic effects of lead and mercury to convince policymakers to take action. Recalling this, and noting the body of evidence starting to accumulate concerning potential impacts of neurotoxins and immunotoxins on human health in terms of increased incidence of PD, autism, asthma, etc., the developmental neurotoxic and immunotoxic parameters added to the proposed Regulation by the European Parliament during the first reading amendments also appear to be warranted.

If it is not possible to limit exposure of pregnant women and young children to such chemicals at levels that would protect brain development, then restricting use of such chemicals to those circumstances where exposure would be negligible is necessary to prevent future harm. Strict regulation could be relaxed at a later stage if later documentation (on the basis of exposure that has already taken place) shows less harm than anticipated.

6.4 The cut-off criteria will provide additional protection for farmers and their families

The cut-off criteria are intended to provide additional health protection for all EU citizens. But they will have the most direct benefit on the farmers and agricultural workers who have the highest risk of pesticide exposures and associated health problems, due to their occupational and environmental situations.

As a number of epidemiological studies cited in this report have found, farmers, agricultural workers and their children are at higher risk of incurring health problems due to long-term exposures to pesticides. The current occupational safety measures appear to provide insufficient protection to this important occupational group and their families. The fact that the people responsible for producing Europe's food must carry this disproportionate risk and the subsequent costs needs to be balanced against any risks of increased food production costs due to reduced availability of certain pesticides.

6.5 Initial economic analysis indicates potential benefits are significant; more economic analysis needed

There is now an extensive body of scientific work that has found statistically sound evidence of strong associations between exposures to pesticides as a group and to specific substances. What are missing are robust economic analyses of the true costs of chronic exposures to chemicals in general and pesticides in particular.

The REACH studies calculating the various benefits that are expected to accrue as the REACH controls are implemented provided important guidance to policy makers. A similar body of economic analysis is now needed to provide more solid information on the current costs to society in terms of the external impacts on human health and the environment from dependence on chemical pesticides for plant protection, as well as on the benefits of reducing exposures.

BIBLIOGRAPHY

Ahlbom, J., Fredriksson, A., Eriksson P., 'Exposure to an organophosphate (DFP) during a defined period in neonatal life induces permanent changes in brain muscarinic receptors and behaviour in adult mice', *Brain Research*, 1995, No 677, pp. 13-19.

Alvanja, M.C., Samanic, C., Dosemeci, M., Lubin, J., Tarone, R., Lynch, C.F., Knott, C., Thomas, K., Hoppin, J.A., Barker, J., Coble, J., Sandler, D.P., Blair, A., 'Use of agricultural pesticides and prostate cancer risk in the agricultural health study cohort', *American Journal of Epidemiology*, 2003, No 157(9), pp. 800-814.

Alguacil, J., Kauppinen, T., Porta, M., Partanen, T., Malats, N., Kogevinas, M., Benavides, F.G., Obiols, J., Bernal, F., Rifa, J., Carrato, A., 'Risk of pancreatic cancer and occupational exposures in Spain (PANKRAS II Study Group)', *Annals of Occupational Hygiene*, 2000, No 44, pp. 391-403.

Andersen, H.R., Nielsen, J.B., Grandjean, P., 'Toxicologic evidence of developmental neurotoxicity of environmental chemicals', *Toxicology*, 2000, No 144, pp. 121-127.

Andlin-Sobocki, P., Jönsson, B., Wittchen, H., Olesen, J., 'Costs of Disorders of the Brain in Europe', *European Journal of Neurology*, 2005, No 12 (Supplement 1).

Arbuckle T.E., Lin Z., Mery L.S., 'An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population', *Environmental Health Perspectives*, 2001, No 109, pp. 851-857.

Arbuckle, T.E., Savitz, D.A., Mery, L.S., Curtis, K.M., 'Exposure to phenoxy herbicides and the risk of spontaneous abortion', *Epidemiology*, 1999, No 10, pp. 752-760.

Baldi, I., Cantegrel, A., Lebailly, P., Tixon, F., Dubroca, B., Chrysostome, V., Dartigues, J.F., Brochard, P., 'Association between Parkinson's disease and exposure to pesticides in southwestern France', *Neuroepidemiology*, 2003, September-October, No 22(5), pp. 305-310.

Baldi, I., et al., 'Delayed Health Effects of Pesticides: Review', *Revue d'Epidémiologie et de Santé Publique*, 1998, No 46(2), pp. 134-142. Also published: ABDC News, Jan 1998, Volume 27, Issue 3.

Baldi, I., Filleul, L., Mohammed-Brahim, B., Fabrigoule, C., Dartigues, J.G., Schwall, S., Drevet, J.P., Salamon, R., Brochard, P. 'Neuropsychologic effects of long-term exposure to pesticides: results from the French Phytoner study', *Environmental Health Perspectives*, 2001, August, No 109(8), pp. 839-844.

Baldi, I., Lebailly, P., Mohammed-Brahim, B., Letenneur, L., Dartigues, J.F., and Brochard, P., 'Neurodegenerative diseases and exposure to pesticides in the elderly', *American Journal of Epidemiology*, 2003, March 1, No 157(5), pp. 409-414.

Baldi, I., Mohammed-Brahim, B., Brochard, P., Dartigues, J.F., Salamon, R. '[Delayed health effects of pesticides : review of current epidemiological knowledge]', *Revue d'épidémiologie et de santé*, 1998, March, No 46(2), pp. 134-142.

Banerjee B.D., Koner B.C., Ray A., 'Immunotoxicity of pesticides: perspective and trends', *Indian Journal of Experimental Biology*, 1996, pp. 723-733.

Bassil, K.L., Vakil, C., Sanborn, M., Cole, D.C., Kaur, J.S., Kerr, K.J., 'Cancer health effects of pesticides: systematic review', *Canadian Family Physician*, 2007, Volume 53, No 10, pp. 1704-1711.

Bearer, C.F., 'How are children different from adults?', *Environmental Health Perspectives*, 1995, Volume 103, Supplement 6, pp. 7-12.

Becher, H., Flesch-Janys, D., Kauppinen, T., Kogevinas, M., Steindorf, K., Manz, A., Wahrendorf, J., 'Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins', *Cancer Causes Control*, 1996, Volume 7, No 3, pp. 312-321.

Berkowitz, G.S., Wetmur, J.G., Birman-Deych, E., Obel, J., Lapinski, R.H., Godbold, J.H., Holzman, I.R., and Wolff, M.S., 'In utero pesticide exposure, maternal paraoxonase activity, and head circumference', *Environmental Health Perspectives*, 2004, March, No 112(3), pp. 388-391.

Bolognesi, C., 'Genotoxicity of pesticides: a review of human biomonitoring studies', *Mutation Research*, 2003, No 543, pp. 251-272.

Bowles R.G. and Webster, J.P.G. "Some problems associated with the analysis of the costs and benefits of pesticides." *Crop Protection* 1995; 14(7): 593-600.

Boyle, C.A., Decoufle, P., Yeargin-Allsopp, M., 'Prevalence and health impact of developmental disabilities in US children', *Pediatrics*, 1994, No 93, pp. 399-403.

Bray F., 'Estimates of cancer incidence and mortality in Europe in 1995', *European Journal of Cancer*, 1995, Volume 38, Issue 1, pp. 99-166.

Brown, T.P., Rumsby, P.C., Capleton, A.C., Rushton, L., Levy, L.D. 'Pesticides and Parkinson's Disease – Is There a Link?', *Environmental Health Perspectives*, 2006, No 114, pp. 156-164.

Buzio, L., Tondel, M., De Palma, G., Buzio, C., Franchini, I., Mutti, A., Axelson, O., 'Occupational risk factors for renal cell cancer. An Italian case-control study,' *Medicina del Lavoro*, 2002, Volume 93, No 4, 2002, pp. 303-309.

Carozza, S.E., Li, B., Elgethun, K., Whitworth, R., 'Risk of childhood cancers associated with residence in agriculturally intense areas in the United States.' *Environmental Health Perspectives*, 2008, Volume 116, No 4, pp. 559-565.

Carozza, S.E., Li, B., Wang, Q., Horel, S., Cooper, S., 'Agricultural pesticides and risk of childhood cancers', *International Journal of Hygiene and Environmental Health*, 2008, July, p. 31.

Claeys, W.L., De Voghel, S., Schmit, J.F., Vromman, V., Pussemier, L., 'Exposure assessment of the Belgian population to pesticide residues through fruit and vegetable consumption', *Food Additives and Contaminants*, 2008, Volume 25, No 5, pp. 851-863.

Clapp, R.W., Jacobs, M.M., Loechler, E.L., 'Environmental and occupational causes of cancer: new evidence 2005-2007', *Review of Environmental Health*, 2008, Volume 23, No 1, pp. 1-37.

Clavel, J., 'Epidémiologie environnementale des cancers,' *La Revue du Praticien-Medcine Generale*, 2007, Volume 31, No 10, pp. 1067-1069.

Cohen, M., 'Environmental toxins and health: The health impacts of pesticides', *Australian Family Physician*, 2007, No 36, pp. 1002-1004.

Cohn, B.A., Wolff, M.S., Cirillo, P.M., Sholtz, R.I., 'DDT and breast cancer in young women: new data on the significance of age at exposure', *Environmental Health Perspectives*, 2007, Volume 115, No 10, pp.1406-1414.

Colosio, C., Barcellini, W., Corsini, E., '[Immunotoxicology in occupational and Environmental medicine: perspectives, limitations and research objectives.]' (article in Italian). *Medicina del Lavoro*, 1998, May-June, No 89(3), pp. 203-205.

Colosio, C., Birindelli, S., Corsini, E., Galli, C.L., Maroni, M., 'Low level exposure to chemicals and the immune system', *Toxicology and Applied Pharmacology*, 2005, September 1; No 207 (2 Suppl), pp. 320-328.

Colosio, C., Corsini, E., Barcellini, W., Maroni, M., 'Immune parameters in biological monitoring of pesticide exposures: current knowledge and perspectives', *Toxicology (Letters)*, 1999, September 5, No 108(2-3), pp. 285-295.

Colosio, C., Tiramani, M., Maroni, M., 'Neurobehavioral Effects of Pesticides: State of the Art', *NeuroToxicology*, 2003, No 24, pp. 577-591.

Corsini, E., Birindelli, S., Fustinoni, S., De Paschale, G., Mammone, T., Visentin, S., Galli, C.L., Marinovich, M., Colosio, C., 'Immunomodulatory effects of the fungicide Mancozeb in agricultural workers', *Toxicology and Applied Pharmacology*, 2005, October 15, No 208 (2), pp. 178-185.

Corsini, E., Codecà, I., Mangiaratti, S., Birindelli, S., Minoia, C., Turci, R., Viviani, B., Facchi, A., Vitelli, N., Lucchi, L., Galli, C.L., Marinovich, M., Colosio, C., 'Immunomodulatory effects of the herbicide propanil on cytokine production in humans: In vivo and in vitro exposure', *Toxicology and Applied Pharmacology*, 2007, July 15, No 222(2), pp. 202-210.

Crisostomo, L., Molina, V.V., 'Pregnancy outcomes among farming households of Nueva Ecija with conventional pesticide use versus integrated pest management', *International Journal of Occupational and Environmental Health*, 2002, No 8, pp. 232-242.

Curl, C.L., Fenske, R.A., Elgethun, K., 'Organophosphorus pesticide exposure of urban and suburban pre-school children with organic and conventional diets', *Environmental Health Perspectives*, 2003, Volume 111, No 3, pp. 337-382.

Daniel, V., Huber, W., Bauer, K., Suesal, C., Mytilineos, J., Melk, A., Conradt, C., Opelz, G., 'Association of elevated blood levels of pentachlorophenol (PCP) with cellular and humoral Immunodeficiencies', *Archives of Environmental & Occupational Health*, 2001, No 5, pp. 77-83.

Davis, J.R., Brownson, R.C., Garcia, R., Bentz, B.J., Turner, A., 'Family pesticide use and childhood brain cancer', *Archives of Environmental Contamination & Toxicology*, 1993, Volume 24, pp. 87-92.

De Roos, A.J., Zahm, S., Cantor, K., Weisenburger, D., Holmes, F., Burmeister, L., Blair, A., 'Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men', *Occupational and Environmental Medicine*, 2003, September, No 60(9), p. E11.

Dich, J., Wiklund, K., 'Prostate cancer in pesticide applicators in Swedish agriculture.' *Prostate*, 1998, Volume 34, pp. 100-112.

Dick, F.D., De Palma, G., Ahmadi, A., Scott, N.W., Prescott, G.J., Bennett, J., Semple, S., Dick, S., Counsell, C., Mozzoni, P., Haites, N., Wettinger, S.G., Mutti, A., Otelea, M., Seaton, A., Söderkvist, P., Felice, A., (Geoparkinson study group), 'Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study', *Occupational and Environmental Medicine*, 2007, October. No 64(10), pp. 666-672. Epub 2007 Mar 1.

Dimich-Ward, H., Hertzman, C., Teschke, K., Hershler, R., Marion, S.A., Ostry, A., et al., 'Reproductive effects of paternal exposure to chlorophenolate wood preservatives in the sawmill industry', *Scandinavian Journal of Work, Environment & Health*, 1996, No 22, pp. 267-273.

Dimich-Ward, H., Hertzman, C., Teschke, K., Hershler, R., Marion, S.A., Ostry, A. et al., 'Reproductive effects of paternal exposure to chlorophenolate wood preservatives in the sawmill industry', *Scandinavian Journal of Work, Environment & Health*, 1996, No 22, pp. 267-273.

Dolapsakis, G., Vlachonikolis, I.G., Varveris, C., Tsatsakis, A.M., 'Mammographic findings and occupational exposure to pesticides currently in use on Crete', *European Journal of Cancer*, 2001, Volume 37, pp. 1531-1536.

Dudimah FD, Odman-Ghazi SO, Hatcher F, Whalen MM. Effect of tributyltin (TBT) on ATP levels in human natural killer (NK) cells: relationship to TBT-induced decreases in NK function. *Journal of Applied Toxicology*. 2007 Jan-Feb;27(1):86-94.

Duramad, P., Tager I.B., Holland N.T., 'Cytokines and other immunological biomarkers in children's environmental health studies', *Toxicology (Letters)*, 2007, July 30, No 172(1-2), pp. 48-49.

Efird, J.T., Holly, E.A., Preston-Martin, S., Mueller, B.A., Lubin, F., Filippini, G., Peris-Bonet, R., McCredie, M., Cordier, S., Arslan, A., Bracci, P.M., 'Farm-related exposures and childhood brain tumours in seven countries: results from the SEARCH International Brain Tumour Study', *Paediatric and Perinatal Epidemiology*, 2003, Volume 17, No 2, pp. 201-211.

Engel, L.S., O'Meara, E.S., Schwartz, S.M., 'Maternal occupation in agriculture and risk of limb defects in Washington State, 1980–1993', *Scandinavian Journal of Work, Environment & Health*, 2000, No 26, pp. 193-198.

Eriksson, M., Hardell, L., Carlberg, M., Akerman, M., 'Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis', *International Journal of Cancer*, 2008, Volume 123, No 7, pp. 1657-1663.

European Commission, 'Commission Staff Working Document on the implementation of the "Community Strategy for Endocrine Disrupters" - a range of substances suspected of interfering with the hormone systems of humans and wildlife', Brussels, 30.11.2007. SEC(2007) 1635 http://ec.europa.eu/environment/endocrine/documents/sec_2007_1635_en.pdf

European Commission, 'Commission Staff Working Paper : Regulation of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restrictions of Chemicals (REACH), establishing a European Chemicals Agency and amending Directive 1999/45/EC and Regulation (EC) {on Persistent Organic Pollutants}: Extended Impact Assessment', SEC (2003) 1171/3.

Fagioli, F., Rigolin, G.M., Cuneo, A., Scapoli, G., Spanedda, R., Cavazzini, P., Castoldi, G., 'Primary gastric lymphoma: distribution and clinical relevance of different epidemiological factors' *Haematologica*, 1994, No 79(3), pp. 213-217.

Faustini, A., Settini, L., Pacifici, R., Fano, V., Zuccaro, P., Forastiere, F., 'Immunological changes among farmers exposed to phenoxy herbicides: preliminary observations', *Occupational and Environmental Medicine*, 1996, No 53, pp. 583-585.

Faustman, E.M., Silbernagel, S.M., Fenske, R.A., Burbacher, T.M., Ponce, R.A., 'Mechanisms Underlying Children's Susceptibility to Environmental Toxicants', *Environmental Health Perspectives*, 2000, Volume 108, Supplement 1, pp. 13-21.

Fear, N.T., Roman, E., Reeves, G., Pannett, B. 'Childhood cancer and paternal employment in agriculture: the role of pesticides', *British Journal of Cancer*, 1998, Volume 77, pp. 825-829.

Ferlay, J., Autier, P., Boniol, M., Heanue, M., Colombet, M., Boyle, P., 'Estimates of the cancer incidence and mortality in Europe in 2006', *Annals of Oncology*, 2007, No 18(3), pp. 581-592.

Ferrís, I., Tortajada, J., Ortega García, J.A., Garcia, I., Castell, J., López Andreu, J.A., Ribes Koninckx, C., Berbel Tornero, O., 'Risks factors for pediatric malignant liver tumors', *Anales de Pediatría*, 2008, Volume 68, No 4, pp. 377-384.

Feychting, M., Plato, N., Nise, N., Ahlbom, A., 'Paternal occupational exposures and childhood cancer', *Environmental Health Perspectives*, 2001, Volume 109, pp. 193-196.

Figa-Talamanca, I., Mearelli, I., Valente, P., Bascherini, S., 'Cancer mortality in a cohort of rural licensed pesticide users in the province of Rome', *International Journal of Epidemiology*, 1993, Volume 22, pp. 579-583.

Fontana, C., Picoco, G., Masala, G., Prastaro, C., Vineis, P., 'Incidence rates of lymphomas and environmental measurements of phenoxy herbicides: Ecological analysis and case-control study', *Archive of Environmental Health*, 1998, No 53, pp. 384-387.

Fuchs, B.A., Sanders, V.M., 'The role of brain-immune interactions in immunotoxicology', *Critical Reviews in Toxicology*, 1994, No 24(2), pp. 151-176.

Galloway, T., Handy, R., 'Immunotoxicity of organophosphorous pesticides', *Ecotoxicology*, 2003, February-August, No 12(1-4), pp. 345-363.

Galvan, C., et al., 'Diagnostic and etiological problems of hydroencephaly', *Ann Esp Pediatr*, 1979, No 12, pp. 529-533.

Ganz M.L. "The lifetime distribution of the incremental societal costs of autism." *Archives of Pediatric and Adolescent Medicine* 2007 Apr; 161(4): 343-9.

- Garry, V.F., 'Pesticides and children', *Toxicology and Applied Pharmacology*, 2004, Volume 198, pp. 152-163.
- Gautier, E., Fortier, I., Courchesne, F., Pepin, P., Mortimer, J., Gauvreau, D., 'Environmental pesticide exposure as a risk factor for Alzheimer's disease: a case-control study', *Environmental Research*, 2001, May, No 86(1), pp. 37-45.
- Ginsberg, G., Hattis, D., Sonawane, B., 'Incorporating pharmacokinetic difference between children and adults in assessing children's risk to environmental toxicants,' *Toxicology and Applied Pharmacology*, 2004, Volume 198, pp. 164-183.
- Goel, A., Aggarwal, P., 'Pesticides Poisoning,' *National Medical Journal of India*, 2002, Volume 20, No 4, pp. 182-191.
- Gordon, J.E., Shy, C.M., 'Agricultural chemical use and congenital cleft lip and/or palate', *Archives of Environmental & Occupational Health*, 1981, No 36, pp. 213-221.
- Grandjean, P., Bellinger, D., Bergman, Å., Cordier, S., et al., 'The Faroes Statement: Human Health Effects of Developmental Exposure to Chemicals in Our Environment', *International Conference on Fetal Programming and Developmental Toxicity*, 2007. <http://www.pptox.dk/Consensus/tabid/72/Default.aspx>
- Grandjean, P., and Weihe, P., 'Developmental origins of environmentally induced disease and dysfunction', (International Conference on Foetal Programming and Developmental Toxicity, Tórshavn, Faroe Islands, 20-24 May, 2007), *Basic & Clinical Pharmacology & Toxicology*, 2008, February, No 102(2), pp. 71-72.
- Grandjean, P., Harari, R., Barr, D.B., Debes, F., 'Pesticides Exposure and Stunting as Independent Predictors of Neurobehavioural Deficits in Ecuadorian School Children', *Pediatrics*, 2006, No 117, pp. 546-556.
- Grandjean, P., White, R., '4. Neurodevelopmental disorders', *Children's health and environment: A review of evidence*, eds, Tamburlini, G., von Ehrenstein, O.S., Bertollini, R., WHO Regional Office for Europe, European Environment Agency, 2002.
- Hagmar, L., Bonassi, S., Stromberg, U., Brogger, A., Knudsen, L.E., Norppa, H., Reuterwell, C., 'Chromosomal aberrations in lymphocytes predict human cancer: a report from the European study group on cytogenetic biomarkers and health (ESCH)', *Cancer Research*, 1998, No 58, pp. 4117-4121.
- Hancock, D.B., Martin, E.R., Mayhew, G.M., Sajich, J.M., Jewett, R., Stacy, M.A., Scott, B.L., Vance, J.M., and Scott, W.K., 'Pesticide exposure and risk of Parkinson's disease: a family-based control study', *BioMedCentral Neurology*, 2008, Mar, No 28(8), p. 6.
- Hansen, E.S., Hasle, H., Lander, F., 'A cohort study on cancer incidence among Danish Gardeners' *American Journal of Industrial Medicine*, 1992, No 21, pp. 651-660.
- Hansen, E.S., Lander, F., and Lauritsen, J.M., 'Time trends in cancer risk and pesticide exposure, a long-term follow-up of Danish gardeners', *Scandinavian Journal of Work, Environment and Health*, 2007, Volume 33, No 6, pp. 465-469.
- Hoffmann, W., Terschüeren, C., Heimpel, H., Feller, A., Butte, W., Hostrup, O., Richardson, D., Greiser, E., 'Population-based research on occupational and environmental factors for leukaemia and non-Hodgkin's lymphoma: the Northern Germany Leukaemia and Lymphoma Study (NLL)', *American Journal of Industrial Medicine*, 2008, Volume 51, No 4, pp. 246-257.
- Holmes, J., Pugner, K., Phillips, R., Dempsey, G., Cayton, H., 'Managing Alzheimer's disease: the cost of care per patient', *British Journal of Healthcare Management*, 1998, No 4, pp. 332-337.
- Hotchkiss, A.K., Rider, C.V., Blystone, C.R., Wilson, V.S., Hartig, P.C., Ankley, G.T., Foster, P.M., Gray, C.L., Gray, L.E., 'Fifteen years after "Wingspread"--environmental endocrine disrupters and human and wildlife health: where we are today and where we need to go', *Toxicological Sciences*, 2008, No 105(2), pp. 235-259.

Hourani, L., Hilton, S., 'Occupational and environmental exposure correlates of adverse live birth outcomes among 1032 US Navy women', *Journal of Occupational and Environmental Medicine*, 2000, No 42, p. 1165.

Idrovo, A.J., Sanín, L.H., 'Adverse reproductive outcomes among women working in Colombian floriculture: a summary of the evidence through meta-analysis', *Biomedica*, 2007, No 27(4), pp. 490-497.

Infante-Rivard, C., Weichenthal, S., 'Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review', *Journal of Toxicology and Environmental Health*, 2007, Part B, Volume 10, No 2, pp. 81-99.

Järbrink, K. "The economic consequences of autistic spectrum disorder among children in a Swedish municipality." *Autism* 2007 Sept; 11(5): 453-63.

Jarrell, J., Gocmen, A., Foster, W., Brant, R., Chan, S., Sevcik, M., 'Evaluation of reproductive outcomes in women inadvertently exposed to hexachlorobenzene in southeastern Turkey in the 1950s', *Reproductive Toxicology*, 1998, No 12, pp. 469-476.

Jarrell, J.F., Gocmen, A., Akyol, D., Brant, R., 'Hexachlorobenzene exposure and the proportion of male births in Turkey 1935-1990', *Reproductive Toxicology*, 2002, No 16, pp. 65-70.

Jönsson, B., 'Revealing the cost of Type II diabetes in Europe', *Diabetologia*, 2002, No 457, pp. S5-S12.

Jönsson, L., Eriksson, M., Kilander, L., Soininen, H., Hallikainen, M., Waldemar, G., Nygaard, H., Andreasen, N., Winblad, B., Wimo, A., 'Determinants of costs of care for patients with Alzheimer's disease', *International Journal of Geriatric Psychiatry*, 2006, No 21(5), pp. 449-459.

Jurewicz, J., Hanke, W., 'Exposure to pesticides and childhood cancer risk: has there been any progress in epidemiological studies?', *International Journal of Occupational Medicine and Environmental Health*, 2006, Volume 19, No 3, pp. 152-169.

Jurewicz, J., Hanke, W., 'Prenatal and childhood exposure to pesticides and neurobehavioral development: review of epidemiological studies', *International Journal of Occupational Medical and Environmental Health*, 2008, Volume 21, No 2, pp. 121-132.

Kang, D., Park, S.K., Beane-Freeman, L., Lynch, C.F., Knott, C.E., Sandler, D.P., Hoppin, J.A., Dosemeci, M., Coble, J., Lubin, J., Blair, A., Alavanja, M., 'Cancer incidence among pesticide applicators exposed to trifluralin in the Agricultural Health Study', *Environmental Research*, 2008, Volume 107, No 2, pp. 271-276.

Karami, S., Boffetta, P., Rothman, N., Hung, R.J., Stewart, T., Zaridze, D., Navritalova, M., Mates, D., Janout, V., Kollarova, H., Bencko, V., Szeszenia-Dabrowska, N., Holcatova, I., Mukeria, A., Gromiec, J., Chanock, S.J., Brennan, P., Chow, W.H., Moore, L.E., 'Renal cell carcinoma, occupational pesticide exposure and modification by glutathione S-transferase polymorphisms.' *Cancer Causes Control*, 2008, Volume 29, No 8, pp. 1567-1571.

Keefe, T.J., Savage, E.P., Munn, S., Wheeler, H.W., *Evaluation of epidemiological factors from two national studies of hospitalized pesticide poisonings, U.S.A.* Exposure Assessment Branch, Hazard Evaluation Division, EPA Office of Pesticides and Toxic Substances, Washington, D.C. (Cited in Pimentel et al., 1992.)

Keifer, M., Rivas, F., Moon, J.D., Checkoway, H., 'Symptoms and cholinesterase activity among rural residents living near cotton fields in Nicaragua', *Occupational and Environmental Medicine*, 1996, No 53, pp. 726-729.

Kettles, M.K., Browning, S.R., Prince, T.S., Horstman, S.W., 'Triazine herbicide exposure and breast cancer incidence: an ecologic study of Kentucky counties', *Environmental Health Perspectives*, 1997, Volume 105, pp. 1222-1227.

- Klein-Schwartz, W., Smith, G.S., 'Agricultural and horticultural chemical poisonings: mortality and morbidity in the United States', *Annals of Emergency Medicine*, 1997, February. No 29(2), pp. 232-238.
- Kricker, A., et al., 'Women and environment: a study of congenital limb anomalies', *Community Health Studies*, 1986, No 10, pp. 1-11.
- Kristensen, P., Andersen, A., Irgens, L.M., Bye, A.S., Sundheim, L., 'Cancer in offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment', *International Journal of Cancer*, 1996, No 65, pp. 39-50.
- Kristensen, P., Andersen, A., Irgens, L.M., Laake, P., Bye, A.S., 'Incidence and risk factors of cancer among men and women in Norwegian agriculture', *Scandinavian Journal of Work and Environmental Health*, 1996, Volume 22, No 1, pp. 14-26.
- Kross, B.C., Burmeister, L.F., Ogilvie, L.K., Fuertes, L.J., Fu, C.M., 'Proportionate mortality study of golf course superintendents', *American Journal of Industrial Medicine*, 1996, Volume 29, pp. 501-506.
- Kumar, S., 'Occupational exposure associated with reproductive dysfunction', *Journal of Occupational Health*, 2004, January, No 46(1), pp. 1-19.
- Kunstadner, P.A., *A Study of Herbicides and Birth Defects in the Republic of Vietnam*, National Academy of Science, Washington, DC, 1982.
- Kunstadner, P., Prapamontol, T., Sirojorn, B.O., Sontirat, A., Tansuhaj, A., Khamboonruang, C., 'Pesticide exposures among Hmong farmers in Thailand', 2001, *International Journal of Occupational and Environmental Health*, No 7(4), pp. 313-325.
- Lackmann, M., Schaller, K.H., Angerer, J., 'Organochlorine compounds in breastfed vs. bottle-fed infants: preliminary results at six weeks of age', *Science of the Total Environment*, 2004, Volume 329, pp. 289-293.
- Landrigan PJ, Schechter CB, Lipton JM, Fahs MC, Schwartz J. "Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities." *Environmental Health Perspectives* 2002 Jul;110(7):721-8.
- Landrigan, P.J., Sonawane, B., Butler, R.N., Trasande, L., Callan, R., and Droller, D., 'Early Environmental Origins of Neurodegenerative Disease in Later Life', *Environmental Health Perspectives*, 2005, September, No 113(9), pp. 1230-1233.
- Lee, WJ et al. "Cancer incidence among pesticide applicators exposed to chlorpyrifos in the Agricultural Health Study," *Journal of the National Cancer Institute* 2004; 96 (23).
- Lee, WJ et al. "Pesticide use and colorectal cancer risk in the Agricultural Health Study," *International Journal of Cancer* 2007; 121: 339-346.
- Levario-Carrillo, M., Feria-Velasco, A., De Celis, R., Ramos-Martinez, E., Cordova-Fierro, L., Solis, F.J., 'Parathion, a cholinesterase-inhibiting plaguicide induces changes in tertiary villi of placenta of women exposed: a scanning electron microscopy study', *Gynecologic and Obstetric Investigation*, 2001, No 52, pp. 269-275.
- Li, Q., 'New mechanism of organophosphorous-induced immunotoxicity', *Journal of Nippon Medical School*, 2007, April, No 74(2), pp. 92-105.
- Lindgren, P., 'Economic evidence in Parkinson's disease: a review', *European Journal of Health Economics*, 2004, Supplement 1, pp. S62-S65.
- Littorin, M., Attewell, R., Skerfving, S., Horstmann, V., Moller, T., 'Mortality and tumour morbidity among Swedish market gardeners and orchardists', *International Archives of Occupational & Environmental Health*, 1993, No 65, pp. 163-169.

Loffredo, C.A., Silbergeld, E.K., Ferencz, C., Zhang, J., 'Association of transposition of the great arteries in infants with maternal exposures to herbicides and rodenticides', *American Journal of Epidemiology*, 2001, No 153, pp. 529-536.

London Food Commission, *Food Adulteration and How to Beat it*, Unwin Paperbacks, London, 1988.

Luzardo, O.P., Goethals, M., Zumbado, M., Alvarez-Leon, E.E., (2 3); Cabrera, F., (1 2); Serra-Majem, L., Boada, L.D., 'Increasing serum levels of non-DDT-derivative organochlorine pesticides in the younger population of the Canary Islands (Spain)', *Science of the Total Environment*, 2006, Volume 367, No 1, pp. 129-138.

Lvovsky, K., et al., 'Health and Environment Strategy Papers', 2001, No1, Working Paper 24096, World Bank.

Ma, X., Buffler, P.A., Gunier, R.B., Dahl, G., Smith, M.T., Reinier, K., Reynolds, P., 'Critical windows of exposure to household pesticides and risk of childhood leukemia', *Environmental Health Perspectives*, 2002, Volume 110, pp. 955-960.

Mathur, V., John, P.J., Soni, I., Bhatnagar, P., 'Blood levels of organochlorine pesticide residues and risk of reproductive tract cancer among women from Jaipur, India', *Advances in Experimental Medicine and Biology*, 2008, Volume 617, No 617, pp. 387-394.

McGlynn, K.A., Quraishi, S.M., Graubard, B.I., Weber, J.P., Rubertone, M.V., Erickson, R.L., 'Persistent organochlorine pesticides and risk of testicular germ cell tumors', *Journal of the National Cancer Institute*, 2008, Volume 100, No 9, 2008, pp. 663-671.

McGovern, V. 'Autism and agricultural pesticides. Integrating data to track trends', *Environmental Health Perspectives*, 2007, October; No 115(10), p. A504.

McGready, R., Simpson, J.A., Htway, M., White, N.J., Nosten, F., Lindsay, S.W., 'A double blind randomized therapeutic trial of insect repellents for the prevention of malaria in pregnancy', *Royal Society of Tropical Medicine and Hygiene*, 2001, No 95, pp. 137-138.

McGready, R., Simpson, J.A., Htway, M., White, N.J., Nosten, F., Lindsay, S.W., 'A double blind randomized therapeutic trial of insect repellents for the prevention of malaria in pregnancy', *Royal Society of Tropical Medicine and Hygiene*, 2001, No 95, pp. 137-138.

Merhi, M., Raynal, H., Cahuzac, E., Vinson, F., Cravedi, J.P., Gamet-Payrastre, L., 'Occupational exposure to pesticides and risk of hematopoietic cancers: meta-analysis of case-control studies.' *Cancer Causes Control*, 2007, Volume 18, No 10, pp. 1209-1226.

Mills, P.K., Yang, R., 'Prostate cancer risk in California farm workers', *Journal of Occupational and Environmental Medicine*, 2003, Volume 45, No 3, pp. 249-258.

Mink, P.J., Adami, H.O., Trichopoulos, D., Britton, N.L., Mandel, J.S., 'Pesticides and prostate cancer: a review of epidemiologic studies with specific agricultural exposure information', *European Journal of Cancer Prevention*, 2008, Volume 17, No 2, pp. 97-110.

Monge, P., Wesseling, C., Guardado, J., Lundberg, I., Ahlbom, A., Cantor, K.P., Weiderpass, E., Partanen, T., 'Parental occupational exposure to pesticides and the risk of childhood leukemia in Costa Rica', *Scandinavian Journal of Work and Environmental Health*, 2007, Volume 33, No 4, pp. 293-303.

Musu, T., *REACHing the workplace. How workers stand to benefit from the new European policy on chemical agents TUTB*, ETUI-REHS, the research institute of the European Trade Union Confederation, 2004.

Nanni, O., Falcini, F., Buiatti, E., Bucchi, L., Naldoni, M., Serra, P., Scarpi, E., Saragoni, L., and Amadori, D., 'Multiple myeloma and work in agriculture: results of a case-control study in Forlì, Italy', *Cancer Causes Control*, 1998, Volume 9, No 3, pp. 277-283.

Natural Resources Defense Council, *Putting Children First: Making Pesticide Levels in Food Safer For Infants and Children*, 1998, <http://www.nrdc.org/health/kids/rpcfsum.asp>

- Newbold R.R., Padilla-Banks E., Jefferson W.N., and Heindel J.J. "Effects of endocrine disruptors on obesity." *International Journal of Andrology*, 2008 Apr; 31(2): 201-8.
- Newcombe, D.S., 'Immune surveillance, organophosphorus exposure, and lymphomagenesis', *Lancet*, 1992, Feb 29, No 339(8792), pp. 539-541.
- Nordby, K.C., Andersen, A., Kristensen, P., 'Incidence of lip cancer in the male Norwegian agricultural population', *Cancer Causes Control*, 2004, Volume 15, No 6, pp. 619-626.
- OECD (Organisation for Economic Co-operation and Development), 'Appraisal of test methods for sex hormone disrupting chemicals', Detailed Review Paper, *OECD Series on Testing and Assessment*, No 21, ENV/JM/MONO(2002)8.
- Osann, K.E., Anton-Culver, T., Kurosaki, T., and Taylor, T., 'Sex difference in lung cancer risk associated with cigarette smoking', *International Journal of Cancer*, 1994, No 54, p. 44.
- Pesticide Action Network UK. Pesticides, Immune Suppression and HIV/AIDS. Food and Farming Briefing No. 5. available on line at https://secure.virtuality.net/panukcom/PDFs/Pesticides_Immune_Suppression_and_HIV_AIDS.pdf
- Peiris-John, R.J., Wickremasinghe, R., 'Impact of low-level exposure to organophosphates on human reproduction and survival', *Royal Society of Tropical Medicine and Hygiene*, 2008, March, No 102(3), pp. 239-245. Epub 2008 Feb 1.
- Perera, F.P., Rauh, V., Tsai, W.Y., Kinney, P., Camann, D., Barr, D., et al., 'Effects of transplacental exposure to environmental pollutants on birth outcomes in a multiethnic population', *Environmental Health Perspective*, 2003, No 111, pp. 201-205.
- Persson, B., 'Occupational exposure and malignant lymphoma', *International Journal of Occupational Medicine and Environmental Health*, 1996, Volume 6, No 9, pp. 309-321.
- Persson, B., Fredriksson, M., Olsen, K., Boeryd, B., Axelson, O., 'Some occupational exposures as risk factors for malignant lymphomas', *Cancer*, 1993, No 72, pp. 1773-1778.
- Phillips, T.M., 'Assessing environmental exposure in children: immunotoxicology screening', *Journal of Exposure Analysis and Environmental Epidemiology*, 2000, No 10, pp. 769-775.
- Pickett, W., King, W.D., Lees, R.E., Bienefeld, M., Morrison, H.I., Brison, R.J., 'Suicide mortality and pesticide use among Canadian farmers', *American Journal of Industrial Medicine*, 1998, No 34, pp. 364-372.
- Pimentel, D., Acquay H., Biltonen, M., Rice, P., Silva, M., Nelson, J., Lipner, V., Giordane, S., Horowitz, A., D'Amore, M. 'Environmental and Economic Costs of Pesticide Use', *Bioscience*, 1992, No 42:10, pp. 750-760.
- Pistl J, Kovalkovicová N, Holovská V, Legáth J, Mikula I. Determination of the immunotoxic potential of pesticides on functional activity of sheep leukocytes in vitro. *Toxicology*. 2003 Jun 3;188(1):73-81.
- Pogoda, J.M., Preston-Martin, S., 'Household pesticides and risk of pediatric brain tumors.' *Environmental Health Perspectives*, 1997, Volume 105, pp. 1214-1220.
- Pottern, L.M., Heineman, E.F., Olsen, J.H., Raffn, E., Blair, A., 'Multiple myeloma among Danish women: employment history and workplace exposures', *Cancer Causes Control*, 1992, Volume 3, No 5, pp. 427-432.
- Pretty J.N., Brett C., Gee D., Hine R.E., Mason C.F., Morison J.I.L., Rayment, M., van der Bijl G., and Dobbs, T. 2001. "Policy challenges and priorities for internalising the externalities of agriculture." *Journal of Environmental Planning and Management* 44 (2): 263-283.
- Provost, D., Cantagrel, A., Lebailly, P., Jaffré, A., Loyant, V., Loiseau, H., Vital, A., Brochard, P., Baldi, I., 'Brain tumours and exposure to pesticides: a case-control study in southwestern France', *Occupational and Environmental Medicine*, 2007, Volume 64, No 8, pp. 509-514.

Queiroz, M.L.S., Fernandes, M.D., Valadares, M.C., 'Neutrophil function in workers exposed to organophosphate and carbamate insecticides', *International Journal of Immunopharmacology*, 1999, Volume 21, Issue 4, April, pp. 263-270.

Repetto, R., Baligia, S., 'Pesticides and immunosuppression: the public health risks', *Health Policy and Public Planning*, 1997, No 12, pp. 97-106.

Repetto R. and Baliga S. *Pesticides and the immune system: the public health risks*. World Resources Institute, Washington DC. March 1996.

Rice, D., Barone, S., 'Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models', *Environmental Health Perspectives*, 2000, Volume 108 (Supplement 3), pp. 511-533.

Rita, P., et al., 'Monitoring of workers occupationally exposed to pesticides in grape gardens in Andhra Pradesh', *Environmental Research and Public Health*, 1987, No 44, pp. 1-5.

Robbins, C., *Poisoned Harvest: A Consumers Guide to Pesticide use and Abuse*, Victor Gollancz Ltd, 1991, pp. 300-313.

Roberts, E.M., English, P.B., Grether, J.K., Windham, G.C., Somberg, L., Wolff, C., 'Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley', *Environmental Health Perspectives*, 2007 October, No 115(10), pp. 1482-1489.

Rodier, P.M., 'Developing Brain as a Target of Toxicity', *Environmental Health Perspectives*, 1995, September, No 103(S6), pp. 73-76.

Rodvall, Y., Ahlbom, A., Spannare, B., Nise, G., 'Glioma and occupational exposure in Sweden, a case-control study', *Occupational & Environmental Medicine*, 1996, Volume 53, pp. 526-537.

Rogan, W.J., Ragan, N.B., 'Some evidence of effects of environmental chemicals on the endocrine system in children', *International Journal of Hygiene and Environmental Health*, 2007, No 210(5), pp. 659-667.

Rohlman, D.S., Arcury, T.A., Quandt, S.A., Lasarev, M., Rothlein, J., Travers, R., Tamulinas, A., Scherer, J., Early, J., Marin, A., Phillips, J., and McCauley, L., 'Neurobehavioral performance in preschool children from agricultural and non-agricultural communities in Oregon and North Carolina', *NeuroToxicology*, 2005, No 26, pp. 589-598.

Roldán-Tapia, L., Parrón, T., Sánchez-Santed, F., 'Neuropsychological effects of long-term organophosphate pesticides', *Neurotoxicology and Teratology*, 2005, March-April, No 27(2), pp. 259-266. Epub 2005 Jan 8.

Rosso, A.L., Hovinga, M.E., Rorke-Adams, L.B., Spector, L.G., Bunin, G.R., 'A case-control study of childhood brain tumors and fathers' hobbies: a Children's Oncology Group study', *Cancer Causes and Control*, 2008.

RPA (Risk and Policy Analysts). *Assessment of the Impact of the New Chemicals Policy on Occupational Health*, Prepared for the European Commission, Environment Directorate-General, 2003.

RPA (Risk and Policy Analysts). *Study on the Benefits of Pesticide Regulation: Final Report for the Pesticide Safety Directorate, Parts 1 & 2* (July 2008).

Rudant, J., Menegaux, F., Leverger, G., Baruchel, A., Nelken, B., Bertrand, Y., Patte, C., Pacquement, H., Vérité, C., Robert, A., Michel, G., Margueritte, G., Gandemer, V., Hémon, D., Clavel, J., 'Household exposure to pesticides and risk of childhood hematopoietic malignancies: The ESCALE study (SFCE)', *Environmental Health Perspectives*, 2007, Volume 115, No 12, pp. 1787-1793.

Rushton et al. *The burden of occupational cancer in Great Britain, Technical Annex 1: Leukaemia*. Imperial College, London: 2007.

Sakazaki H., Ueno H., Umetani K., Utsumi H., Nakamuro K. 2001. Immunological evaluation of environmental chemicals utilizing mouse lymphocyte mitogenesis test. *Journal of Health Science*, 47(3) 258-271.

Salehi, F., Dunfield, L., Phillips, K.P., Krewski, D. and Vanderhyden ,B.C., ‘ Risk factors for ovarian cancer: an overview with emphasis on hormonal factors’, *Journal of Toxicology and Environmental Health*, 2008, Volume 11, Nos 3-4, pp. 301-321.

Salehi, F., Turner, M.C., Phillips, K.P., Wigle, D.T., Krewski, D., Aronson, K.J., ‘Review of the etiology of breast cancer with special attention to organochlorines as potential endocrine disruptors’, *Journal of Toxicology and Environmental Health B*, 2008, Volume 11, Nos 3-4, pp. 276-300.

Samarawickrema, N., Pathmeswaran, A., Wickremasinghe, R., Peiris-John, R., Karunaratna, M., Buckley, N., Dawson, A., de Silva, J., ‘Fetal effects of environmental exposure of pregnant women to organophosphorus compounds in a rural farming community in Sri Lanka’, *Clinical toxicology (Philadelphia, Pa.)*, 2008, July, No 46(6), pp. 489-495.

Sanborn, M., Cole, D., Kerr, K., Vakil, C., Sanin, L.H., and Basil, K., *Systematic Review of Pesticides Human Health Effects*, The Ontario College of Family Physicians, 2004. <http://www.ocfp.on.ca/local/files/Communications/Current%20Issues/Pesticides/Final%20Paper%2023APR2004.pdf>

Sanborn, M., Kerr, K.J., Sanin, L.H., Cole, D.C., Bassil, K.L., Vakil, C., ‘Non-cancer health effects of pesticides: systematic review and implications for family doctors’, *Canadian Family Physician*, 2007, October, No 53(10), pp. 1712-1720.

Santibáñez, M., Bolumar, F., and Garcia, A.M., ‘Occupational risk factors in Alzheimer’s disease: a review assessing the quality of published epidemiological studies’, *Journal of Occupational and Environmental Medicine*, 2007, November, No 64(11), pp. 723-732.

Savitz, D.A., Arbuckle, T.E., Kaczor, D., Curtis, K.M., ‘Male pesticide exposure and pregnancy outcome’, *American Journal of Epidemiology*, 1997, No 146, pp. 1025-1036.

Scheife, R.T., Schumock, G.T., Burstein, A., Gottwald, M.D., Luer, M.S., ‘Impact of Parkinson's disease and its pharmacologic treatment on quality of life and economic outcomes’, *American Journal of Health-System Pharmacy*, 2000, Volume 57, Issue 10, pp. 953-962.

Settimi, L., Masina, A., Andron, A., Axelson, O., ‘Prostate cancer and exposure to pesticides in agricultural settings’, *International Journal of Cancer*, 2003, No 104, pp. 458-461.

Sharma-Wagner, S., Chokkalingam, A.P., Malaker, H.S., Stone, B.J., McLaughlin, J.K., Hsing, A.W., ‘Occupation and prostate cancer risk in Sweden’, *Journal of Occupational & Environmental Medicine*, 2000, No 42, pp. 517-525.

Sharpe, C.R., Franco, E.L., de Camargo, B., Lopes, L.F., Barreto, J.H., Johnsson, R.R., Mauad, M.A., ‘Parental exposures to pesticides and risk of Wilms’ tumor in Brazil’, *American Journal of Epidemiology*, 1995, No 141, pp. 210-217.

Sharma-Wagner, S., Chokkalingam, A.P., Malaker, Hans, S.R., Stone, B.J., McLaughlin, J.K., Hsing, A.W., ‘Occupation and Prostate Cancer Risk in Sweden’, *Journal of Occupational & Environmental Medicine*, 2000, No 42, pp. 517-525.

Simcox, N.J., Fenske, R.A., Wolz S.A., Lee, I.C., Kalman, D., ‘Pesticides in household dust and soil: exposure pathways for children of agricultural families’, *Environmental Health Perspectives*, 1995, Volume 103, No 12, pp.1126-1134.

Soerjomataram I., de Vries E., Pukkala E., Coebergh J.W., ‘Excess of cancers in Europe: A study of eleven major cancers amenable to lifestyle change’, *International Journal of Cancer*, 2006, No 120 6, pp. 1336-1343.

Solis, F.J., 'Parathion, a cholinesterase-inhibiting plaguicide induces changes in tertiary villi of placenta of women exposed: a scanning electron microscopy study', *Gynecologic and Obstetric Investigation*, 2001, No 52, pp. 269-275.

Solomon, G., *Pesticides and Human Health: A Resource for Health Care Professionals*, Physicians for Social Responsibility and Californians for Pesticide Reform, 2000.

Solomon, G., Weiss, P., 'Chemical contaminants in breast milk: time trends and regional variability,' *Environmental Health Perspectives*, 2002, Volume 110, No 6, pp. 339-347.

Spinelli, J.J., Ng, C.H., Weber, J.P., Connors, J.M., Gascoyne, R.D., Lai, A.S., Brooks-Wilson, A.R., Le, N.D., Berry, B.R., Gallagher, R.P., 'Organochlorines and risk of non-Hodgkin lymphoma', *International Journal of Cancer*, 2007, Volume 121, No 12, pp. 2767-2775.

Swaen, G.M., van Amelsvoort, L.G., Slangen, J.J., Mohren, D.C., 'Cancer mortality in a cohort of licensed herbicide applicators', *International Archives of Occupational Environmental Health*, 2004, Volume 77, No 4, pp. 293-295.

Tamburlini, G., von Ehrenstein, O., Bertollini, R., eds. *Children's Health and Environment*, Copenhagen, Denmark: European Environment Agency; 2002, pp. 66-78 (Environmental Issue Report No 29).

Taylor R.T., Tucker T., Whalen M.M. Persistent inhibition of human natural killer cell function by ziram and pentachlorophenol. *Environmental Toxicology* 2005 Aug;20(4):418-24.

Taylor TR, Whalen MM. Effects of ziram on tumor-cell-binding capacity, cell-surface marker expression, and ATP levels of human natural killer cells. *Cell Biology and Toxicology*. 2008 Aug 1.

The Times, 'Parents of boy without eyes sue American chemical giant', 6th December, 1994.

Trasande L., Landrigan PJ, Schechter C. "Public health and economic consequences of methyl mercury toxicity to the developing brain." *Environmental Health Perspectives* 2005 May; 113(5): 590-596.

Tryphonas, H., 'Approaches to detecting immunotoxic effects of environmental contaminants in humans', *Environmental Health Perspectives*, 2001, December; No 109(Suppl 6), pp. 877-884.

Tüchsen, F., Jensen, A.A., 'Agricultural work and the risk of Parkinson's disease in Denmark, 1981-1993', *Scandinavian Journal of Work, Environment and Health*, 2000, August, No 26(4), pp. 359-362.

Valery, P.C., McWhirter, W., Sleight, A., Williams, G., Bain, C., 'Farm exposures, parental occupation, and risk of Ewing's sarcoma in Australia: a national case-control study', *Cancer Causes Control*, 2002, Volume 13, No 3, pp. 263-270.

Van Leeuwen, J.A., Waltner-Toews, D., Abernathy, T., Smit, B., Shoukri, M., 'Associations between stomach cancer incidence and drinking water contamination with atrazine and nitrate in Ontario (Canada) agroecosystems, 1987-1991', *International Journal of Epidemiology*, 1999, No 28, pp. 836-840.

Van Maele-Fabry, G., Duhayon, S., Mertens, C., Lison, D., 'Risk of leukaemia among pesticide manufacturing workers: a review and meta-analysis of cohort studies', *Environmental Research*, 2008, Volume 106, No 1, pp. 121-137.

Van Wijngaarden, E., 'Mortality of mental disorders in relation to potential pesticide exposure', *Journal of Occupational and Environmental Medicine*, 2003, No 45(5), pp. 564-568.

Van Wijngaarden, E., Stewart, P.A., Olsham, A.F., Savitz, D.A., Bunin, G.R., 'Parental occupational exposure to pesticides and childhood brain cancer', *American Journal of Epidemiology*, 2003, No 157, pp. 989-997.

Viel, J.F., Challier, B., Pitard, A., Pobel, D., 'Brain cancer mortality among French farmers: the vineyard pesticide hypothesis', *Archives of Environmental Health*, 1998, No 53, pp. 65-70.

- Viel, J.F., Richardson, S.T., 'Lymphoma, multiple myeloma and leukaemia among French farmers in relation to pesticide exposure', *Social Science and Medicine*, 1993, Volume 37, No 6, pp. 771-777.
- Voccia, I., Blakley, B., Brousseau, P., Fournier, M., 'Immunotoxicity of pesticides : a review', *Toxicology and Industrial Health*, 1999, January-March, No 15(1-2), pp. 119-132.
- Vos, J.G., Dybing, E., Greim, H.A., Ladefoged, O., Lambré, C., Tarazona, J.V., Brandt, I., Vethaak, A.D., 'Health effects of endocrine-disrupting chemicals on wildlife, with special reference to the European situation', *Critical Reviews in Toxicology*, 2000, No 30(1), pp. 71-133.
- Waibel H., Fleischer G., and Becker H. 1999a. "The economic benefits of pesticides: A case study from Germany." *Agrarwirtschaft* 48 H. 6: 219-230.
- Waibel H., Fleischer G., and Becker H. 1999b. "Cost-benefit analysis of pesticides." *Agrarwirtschaft* 48 H. 8/9: 338-342.
- Wancata, J., Musalek, M., Alexandrowicz, R., Krautgartner, M., 'Number of dementia sufferers in Europe between the years 2000 and 2050', *European Psychiatry*, 2003, Volume 18, Issue 6, pp 306-313.
- Wanless, D., *Securing Our Future Health: Taking a Long-Term View*, 2002, HM Treasury, London, p. 25.
- Waterhouse, D., Carman, W.J., Schottenfeld, D., Gridley, G., McLean, S., 'Cancer incidence in the rural community of Tecumseh, Michigan: a pattern of increased lymphopietic neoplasms', *Cancer*, 1996, No 77(4), pp. 763-770.
- Weselak, M., Arbuckle, T.E., Foster, W., 'Pesticide exposures and developmental outcomes: the epidemiological evidence', *Journal of Toxicology and Environmental Health*, 2007, Part B, Volume 10, Issue 1 & 2, pp. 41-80.
- Weselak, M., Arbuckle, T.E., Wigle, D.T. and Krewski, D., 'In utero pesticide exposure and childhood morbidity', *Environmental Research*, 2007, Volume 103, No 1, pp. 79-86.
- Whalen, M.M., Bommanna, G., Loganathan., Yamashita N., Saito, T., 'Immunomodulation of human natural killer cell cytotoxic function by triazine and carbamate pesticides', *Chemico-Biological Interactions*, 2003, Volume 145, Issue 3, 15 June 2003, pp. 311-319.
- Whalen MM, Loganathan BG, Yamashita N, Saito T. "Immunomodulation of human natural killer cell cytotoxic function by triazine and carbamate pesticides." *Chemico-Biological Interactions*. 2003 Jun 15;145(3):311-9.
- Whyatt, R.M., Rauh, V., Barr, D.B., Camann, D.E., Andrews, H.F., Garfinkel, R., Hoepner, L.A., Diaz, D., Dietrich, J., Reyes, A., Tang, D., Kinney, P.L., and Perera, F.P., 'Prenatal insecticide exposures and birth weight and length among an urban minority cohort', *Environmental Health Perspectives*, 2004, July, No 112(10), pp. 1125-1132.
- Wigle, D.T., Arbuckle, T.E., Turner, M.C., Brub, A., Yang, O., Liu, S., Krewski, D., 'Epidemiologic Evidence of Relationships Between Reproductive and Child Health Outcomes and Environmental Chemical Contaminants', *Journal of Toxicology and Environmental Health*, 2008, May, Part B, Volume 11, Issue 5 & 6, pp. 373-517.
- Wiles, R., Davies, K., Campbell, C., *Overexposed: Organophosphate Insecticides in Children's Food*, Environmental Working Group, 1998.
- Wilson, S., Dzon, L., Reed, A., Pruitt, M., Whalen, M.M., 'Effects of in vitro exposure to low levels of organotin and carbamate pesticides on human natural killer cell cytotoxic function', *Environmental Toxicology*, 2004, December, No 19(6), pp. 554-563.
- Windham G., Fenster L., 'Environmental contaminants and pregnancy outcomes', *Fertility and Sterility*, 2008 February, No 89 (2 Supplement), pp. e111-116.
- Wolff, M.S., Engel, S., Berkowitz, G., Teitelbaum, S., Siskind, J., Barr, D.B., Wetmur, J. 'Prenatal pesticide and PCB exposures and birth outcomes', *Pediatric Research*, 2007, February, No 61(2), pp. 243-250.

Xia, Y., Cheng, S., Bian, Q., Xu, L., Collins, M.D., Chang, H.C., Song, L., Liu, J., Wang, S., Wang, X., 'Genotoxic effects on spermatozoa of carbaryl-exposed workers', *Toxicological Sciences*, 2005, No 85(1), pp. 615-623. Epub 2004 Dec 22.

Young, J.G., Eskenazi, G., Gladstone, E.A., Bradman, A., Pedersen, L., Johnson, C., Barr, D.B., Furlong, C.E., Holland, N.T., 'Association between *in utero* organophosphate pesticide exposure and abnormal reflexes in neonates', *NeuroToxicology*, 2005, No 26, pp. 199-229.

Zahm, S.H., Ward, M.H., 'Pesticides and childhood cancers', *Environmental Health Perspectives*, 1998, No 106, pp. 893-908.

Zumbado, M., Goethals, M., Alvarez-León, E.E., Luzardo, O.P., Cabrera, F., Serra-Majem, L., Domínguez-Boada, L., 'Inadvertent exposure to organochlorine pesticides DDT and derivatives in people from the Canary Islands (Spain)', *Science of the Total Environment*, 2005, Volume 339, Nos 1-3, pp. 49-62.

ANNEX I

Directive 67/548/EEC's criteria for classification on the basis of specific effects on human health

ANNEX VI

GENERAL CLASSIFICATION AND LABELLING REQUIREMENTS FOR DANGEROUS SUBSTANCES AND PREPARATIONS**Contents**

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4. CLASSIFICATION ON THE BASIS OF SPECIFIC EFFECTS ON HUMAN HEALTH
 - 4.1. **Introduction**
 - 4.1.1. This chapter sets out the procedure for the classification of substances which may have the effects mentioned below. For preparations see section 4.2.4.
 - 4.1.2. If a manufacturer, distributor or importer has information available which indicates that a substance should be classified and labelled in accordance with the criteria given in section 4.2.1, 4.2.2 or 4.2.3, he shall provisionally label the substance in accordance with these criteria, on the basis of the assessment of the evidence by a competent person.

- 4.1.3. The manufacturer, distributor or importer shall submit as soon as possible a document summarising all relevant information to one Member State in which the substance is placed on the market. Relevant information in this context comprises in particular all available published and unpublished information required for appropriate classification of the substance in question, on the basis of the intrinsic properties according to the categories laid down in Article 2(2) and in accordance with the criteria in this Annex. The submitted summary document should include a bibliography containing all relevant references, including any relevant unpublished data.
- 4.1.4. Furthermore, a manufacturer, distributor or importer who has new data which are relevant to the classification and labelling of a substance in accordance with the criteria given in section 4.2.1, 4.2.2 or 4.2.3, shall submit this data as soon as possible to one Member State in which the substance is placed on the market.
- 4.1.5 To obtain as quickly as possible a harmonised classification for the Community by the procedure defined in Article 28 of this Directive, Member States which have relevant information available justifying the classification of a substance in one of these categories, whether submitted by the manufacturer or not, should forward such information together with suggestions for classification and labelling, to the Commission as soon as possible.

The Commission will forward to the other Member States the classification and labelling proposal that it receives. Any Member State may ask the Commission for the information it has received.

Any Member State which has good reason to believe that the suggested classification and labelling is inappropriate as far as the carcinogenic, mutagenic or reproductive toxicity effects are concerned shall notify the Commission thereof.

4.2. Criteria for classification, indication of danger, choice of risk phrases

4.2.1. Carcinogenic substances

For the purpose of classification and labelling, and having regard to the current state of knowledge, such substances are divided into three categories:

Category 1

Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

Category 2

Substances which should be regarded as if they are carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:

- appropriate long-term animal studies,
- other relevant information.

Category 3

Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in category 2.

4.2.1.1. *The following symbols and specific risk phrases apply:*

Categories 1 and 2:

Substances classified carcinogenic category 1 or 2 shall be assigned the symbol 'T' and the risk phrase

R45 May cause cancer

However, substances and preparations which present a carcinogenic risk only when inhaled, for example, as dust, vapour or fumes, (other routes of exposure e.g. by swallowing or in contact with skin do not present any carcinogenic risk), shall be assigned the symbol 'T' and the risk phrase

R49 May cause cancer by inhalation

Categories 3:

Substances classified as carcinogenic category 3 shall be assigned the symbol 'Xn' and the risk phrase

R40 Limited evidence of a carcinogenic effect

4.2.1.2. *Comments regarding the categorisation of carcinogenic substances*

The placing of a substance into category 1 is done on the basis of epidemiological data; placing into categories 2 and 3 is based primarily on animal experiments.

For classification as a category 2 carcinogen either positive results in two animal species should be available or

clear positive evidence in one species, together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

Category 3 actually comprises 2 subcategories:

- (a) substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in category 2. Additional experiments would not be expected to yield further relevant information with respect to classification;
- (b) substances which are insufficiently investigated. The available data are inadequate, but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

For a distinction between categories 2 and 3 the arguments listed below are relevant which reduce the significance of experimental tumour induction in view of possible human exposure. These arguments, especially in combination, would lead in most cases to classification in category 3, even though tumours have been induced in animals:

- carcinogenic effects only at very high dose levels exceeding the 'maximal tolerated dose'. The maximal tolerated dose is characterised by toxic effects which, although not yet reducing lifespan, go along with physical changes such as about 10 % retardation in weight gain,
- appearance of tumours, especially at high dose levels, only in particular organs of certain species known to be susceptible to a high spontaneous tumour formation,
- appearance of tumours, only at the site of application, in very sensitive test systems (e.g. i.p. or s.c. application of certain locally active compounds), if the particular target is not relevant to man,
- lack of genotoxicity in short-term tests in vivo and in vitro,
- existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g., hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation),
- existence of a species-specific mechanism of tumour formation (e.g. by specific metabolic pathways) irrelevant for man.

For a distinction between category 3 and no classification arguments are relevant which exclude a concern for man:

4.2.2.1. For the purposes of classification and labelling, and having regard to the current state of knowledge, such substances are divided into three categories:

- a substance should not be classified in any of the categories if the mechanism of experimental tumour formation is clearly identified, with good evidence that this process cannot be extrapolated to man,
- if the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories,
- particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence.

4.2.2 Mutagenic substances

Category 1

Substances known to be mutagenic to man.

There is sufficient evidence to establish a causal association between human exposure to a substance and heritable genetic damage.

Category 2

Substances which should be regarded as if they are mutagenic to man.

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in the development of heritable genetic damage, generally on the basis of:

- appropriate animal studies,
- other relevant

information. Category 3

Substances which cause concern for man owing to possible mutagenic effects. There is evidence from appropriate mutagenicity studies, but this is insufficient to place the substance in category 2.

4.2.2.2. *The following symbols and specific risk phrases apply:*

Categories 1 and 2:

Substances classified as mutagenic category 1 or 2 shall be assigned the symbol 'T' and the risk phrase

R46 May cause heritable genetic damage

Categories 3:

Substances classified as mutagenic category 3 shall be assigned the symbol 'M' and the risk phrase

R68 Possible risk of irreversible effects.

4.2.2.3. *Comments regarding the categorisation of mutagenic substances*

Definition of terms:

A mutation is a permanent change in the amount or structure of the genetic material in an organism, resulting in a change of the phenotypic characteristics of the organism. The alterations may involve a single gene, a block of genes, or a whole chromosome. Effects involving single genes may be a consequence of effects on single DNA bases (point mutations) or of large changes, including deletions, within the gene. Effects on whole chromosomes may involve structural or numerical changes. A mutation in the germ cells in sexually reproducing organisms may be transmitted to the offspring. A mutagen is an agent that gives rise to an enhanced occurrence of mutations.

It should be noted that substances are classified as mutagens with specific reference to inherited genetic damage. However, the type of results leading to classification of chemicals in category 3: 'induction of genetically relevant events in somatic cells' is generally also regarded as an alert for possible carcinogenic activity.

Method development for mutagenicity testing is an ongoing process. For many new tests no standardised protocols and evaluation criteria are presently available. For the evaluation of mutagenicity data the quality of the test performance and the degree of validation of the test method have to be considered.

Category 1

To place a substance in category 1, positive evidence from human mutation epidemiology studies will be needed. Examples of such substances are not known to date. It is recognised that it is extremely difficult to obtain reliable information from studies on the incidence of mutations in human populations, or on possible increases in their frequencies.

Category 2

To place a substance in category 2, positive results are needed from assays showing (a) mutagenic effects, or (b) other cellular interactions relevant to mutagenicity, in germ cells of mammals *in vivo*, or (c) mutagenic effects in somatic cells of mammals *in vivo* in combination with clear evidence that the substance or a relevant metabolite reaches the germ cells.

With respect to placement in category 2, at present the following methods are appropriate:

2(a) *In vivo* germ cell mutagenicity assays:

- specific locus mutation test,
- heritable translocation test,
- dominant lethal mutation test.

These assays actually demonstrate the appearance of affected progeny or a defect in the developing embryo.

^{2 (b)} *In vivo* assays showing relevant interaction with germ cells (usually DNA):

- assays for chromosomal abnormalities, as detected by cytogenetic analysis, including aneuploidy, caused by malsegregation of chromosomes,
- test for sister chromatid exchanges (SCEs),
- test for unscheduled DNA synthesis (UDS),
- assay of (covalent) binding of mutagen to germ cell DNA,
- assaying other kinds of DNA damage.

These assays provide evidence of a more or less indirect nature. Positive results in these assays would normally be supported by positive results from in vivo somatic cell mutagenicity assays, in mammals or in man (see under category 3, preferably methods as under 3(a)).

2(c) In vivo assays showing mutagenic effects in somatic cells of mammals (see under 3(a)), in combination with toxicological methods, or other methodologies capable of demonstrating that the compound or a relevant metabolite reaches the germ cells.

For 2(b) and 2(c), positive results from host-mediated assays or the demonstration of unequivocal effects in in vitro assays can be considered as supporting evidence.

Category 3

To place a substance in category 3, positive results are needed in assays showing (a) mutagenic effects or (b) other cellular interaction relevant to mutagenicity, in somatic cells in mammals in vivo. The latter especially would normally be supported by positive results from in vitro mutagenicity assays.

For effects in somatic cells in vivo at present the following methods are appropriate:

3(a) In vivo somatic cell mutagenicity assays:

- bone marrow micronucleus test or metaphase analysis,
- metaphase analysis of peripheral lymphocytes,
- mouse coat colour spot test.

3(b) In vivo somatic cell DNA interaction assays:

- test for SCEs in somatic cells,
- test for UDS in somatic cells,
- assay for the (covalent) binding of mutagen to somatic cell DNA,
- assay for DNA damage, e.g. by alkaline elution, in somatic cells.

Substances showing positive results only in one or more in vitro mutagenicity assays should normally not be classified. Their further investigation using in vivo assays, however, is strongly indicated. In exceptional cases, e.g. for a substance showing pronounced responses in several in vitro assays, for which no relevant in vivo data are available, and which shows resemblance to known mutagens, classification in category 3 could be considered.

4.2.3. Substances toxic to reproduction

4.2.3.1. For the purposes of classification and labelling and having regard to the present state of knowledge, such substances are divided into three categories:

Category 1

Substances known to impair fertility in humans

There is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility.

Substances known to cause developmental toxicity in humans

There is sufficient evidence to establish a causal relationship between human exposure to the substance and subsequent developmental toxic effects in the progeny.

Category 2

Substances which should be regarded as if they impair fertility in humans

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in impaired fertility on the basis of:

- clear evidence in animal studies of impaired fertility in the absence of toxic effects, or, evidence of impaired fertility occurring at around the same dose levels as other toxic effects but which is not a secondary non-specific consequence of the other toxic effects,
- other relevant information.

Substances which should be regarded as if they cause developmental toxicity to

humans

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in developmental toxicity, generally on the basis of:

- clear results in appropriate animal studies where effects have been observed in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects,
- other relevant information.

Category 3

Substances which cause concern for human fertility

Generally on the basis of:

- results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of impaired fertility in the absence of toxic effects, or evidence of impaired fertility occurring at around the same dose levels as other toxic effects, but which is not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in category 2,
- other relevant information.

Substances which cause concern for humans owing to possible developmental toxic effects

Generally on the basis of:

- results in appropriate animal studies which provide sufficient evidence to cause a strong suspicion of developmental toxicity in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects, but where the evidence is insufficient to place the substance in category 2,
- other relevant information.

4.2.3.2. *The following symbols and specific risk phrases apply:*

Category 1:

for substances that impair fertility in humans:

Substances classified as toxic to reproduction category 1 shall be assigned the symbol 'T' and the risk phrase

R60 May impair fertility

for substances that cause developmental toxicity:

Substances classified as toxic to reproduction category 1 shall be assigned the symbol 'T' and the risk phrase

R61 May cause harm to the unborn child

Category 2:

for substances that should be regarded as if they impair fertility in humans:

Substances classified as toxic to reproduction category 2 shall be assigned the symbol 'T' and the risk phrase

R60 May impair fertility

for substances that should be regarded as if they cause developmental toxicity in humans:

Substances classified as toxic to reproduction category 2 shall be assigned the symbol 'T' and the risk phrase

R61 May cause harm to the unborn child

Category 3:

for substances which cause concern for human fertility:

Substances classified as toxic to reproduction category 3 shall be assigned the symbol 'Xn' and the risk phrase

R62 Possible risk of impaired fertility

for substances which cause concern for humans owing to possible developmental toxic effects:

Substances classified as toxic to reproduction category 3 shall be assigned the symbol 'Xn' and the risk phrase

R63 Possible risk of harm to the unborn child.

4.2.3.3. *Comments regarding the categorisation of substances toxic to reproduction*

Reproductive toxicity includes impairment of male and female reproductive functions or capacity and the induction of non-inheritable harmful effects on the progeny. This may be classified under two main headings of 1. Effects on male or female fertility; 2. Developmental toxicity.

1 Effects on male or female fertility, includes adverse effects on libido, sexual behaviour, any aspect of spermatogenesis or oogenesis, or on hormonal activity or physiological response which would interfere with the capacity to fertilise, fertilisation itself or the development of the fertilised ovum up to and including implantation.

2 Developmental toxicity, is taken in its widest sense to include any effect interfering with normal development, both before and after birth. It includes effects induced or manifested prenatally as well as those manifested postnatally. This includes embryotoxic / ifetotoxic effects such as reduced body weight, growth and developmental retardation, organ toxicity, death, abortion, structural defects (teratogenic effects), functional defects, peri-postnatal defects, and impaired postnatal mental or physical development up to and including normal pubertal development.

Classification of chemicals as toxic to reproduction is intended to be used for chemicals which have an intrinsic or specific property to produce such toxic effects. Chemicals should not be classified as toxic to reproduction where such effects are solely produced as a non-specific secondary consequence of other toxic effects. Chemicals of most concern are those which are toxic to reproduction at exposure levels which do not produce other signs of toxicity.

The placing of a compound in category 1 for effects on fertility and/or developmental toxicity is done on the basis of epidemiological data. Placing in categories 2 or 3 is done primarily on the basis of animal data. Data from in vitro studies, or studies on avian eggs, are regarded as 'supportive evidence' and would only exceptionally lead to classification in the absence of in vivo data.

In common with most other types of toxic effect, substances demonstrating reproductive toxicity will be expected to have a threshold below which adverse effects would not be demonstrated. Even when clear effects have been demonstrated in animal studies the relevance for humans may be doubtful because of the doses administered, for example, where effects have been demonstrated only at high doses, or where marked toxicokinetic differences exist, or the route of administration is inappropriate. For these or similar reasons it may be that classification in category 3, or even no classification, will be warranted.

Annex V to the Directive specifies a limit test in the case of substances of low toxicity. If a dose level of at least 1 000 mg/kg orally produces no evidence of effects toxic to reproduction, studies at other dose levels may not be considered necessary. If data are available from studies carried out with doses higher than the above limit dose, this data must be evaluated together with other relevant data. Under normal circumstances it is considered that effects seen only at doses in excess of the limit dose would not necessarily lead to classification as 'Toxic to reproduction'.

EFFECTS ON FERTILITY

For the classification of a substance in category 2 for impaired fertility, there should normally be clear evidence in one animal species, with supporting evidence on mechanism of action or site of action, or chemical relationship to other known anti-fertility agents or other information from humans which would lead to the conclusion that effects would be likely to be seen in humans. Where there are studies in only one species without other relevant supporting evidence then classification in category 3 may be appropriate.

Since impaired fertility may occur as a non-specific accompaniment to severe generalised toxicity or where there is severe inanition, classification in category 2 should only be made where there is evidence that there is some degree of specificity of toxicity for the reproductive system. If it was demonstrated that impaired fertility in animal studies was due to failure to mate, then for classification in category 2, it would normally be necessary to have evidence on the mechanism of action in order to interpret whether any adverse effect such as alteration in pattern of hormonal release would be likely to occur in humans.

DEVELOPMENTAL TOXICITY

For classification in category 2 there should be clear evidence of adverse effects in well conducted studies in one or more species. Since adverse effects in pregnancy or postnatally may result as a secondary consequence of maternal toxicity, reduced food or water intake, maternal stress, lack of maternal care, specific dietary deficiencies, poor animal husbandry, intercurrent infections, and so on, it is important that the effects observed should occur in well conducted studies and at dose levels which are not associated with marked maternal toxicity. The route of exposure is also important. In particular, the injection of irritant material intraperitoneally may result in local damage to the uterus and its contents, and the results of such studies must be interpreted with caution and on their own would not normally lead to classification.

Classification in category 3 is based on similar criteria as for category 2 but may be used where the experimental design has deficiencies which make the conclusions less convincing, or where the possibility that the effects may have been due to non-specific influences such as generalised toxicity cannot be excluded.

In general, classification in category 3 or no category would be assigned on an ad hoc basis where the only effects recorded are small changes in the incidences of spontaneous defects, small changes in the proportions of common variants such as are observed in skeletal examinations, or small differences in postnatal developmental assessments.

Effects during lactation

Substances which are classified as toxic to reproduction and which also cause concern due to their effects on lactation should in addition be labelled with R64 (see criteria in section 3.2.8).

For the purpose of classification, toxic effects on offspring resulting only from exposure via the breast milk, or toxic effects resulting from direct exposure of children will not be regarded as 'Toxic to reproduction', unless such effects result in impaired development of the offspring.

Substances which are not classified as toxic to reproduction but which cause concern due to toxicity when transferred to the baby during the period of lactation should be labelled with R64 (see criteria in section 3.2.8). This R-phrase may also be appropriate for substances which affect the quantity or quality of the milk.

R64 would normally be assigned on the basis of:

- (a) toxicokinetic studies that would indicate the likelihood that the substance would be present in potentially toxic levels in breast milk; and/or
- (b) on the basis of results of one or two generation studies in animals which indicate the presence of adverse effects on the offspring due to transfer in the milk; and/or
- (c) on the basis of evidence in humans indicating a risk to babies during the lactational period.

Substances which are known to accumulate in the body and which subsequently may be released into milk during lactation may be labelled with R33 and R64

ANNEX II: Which pesticides would be affected by the cut – off criteria?

The Common Position reached by the Council of Ministers in June 2008 sets several health-based cut-off criteria for deciding whether an active substance (AS) should be permitted for use in plant protection products in the EU. These cut-off criteria are found in Section 3.6 of the proposed Regulation's Annex on "Procedure and criteria for the approval of active substances, safeners and synergists pursuant to Chapter II", which deals with human health protection. They provide that an active substance shall only be approved if:

- it is not classified as a *mutagen category 1 or 2* (section 3.6.2).
- it is not classified as a *carcinogen category 1 or 2* unless the exposure of humans under realistic proposed conditions of use is negligible (section 3.6.3).
- if it is not classified as a *toxic for reproduction category 1 or 2* unless the exposure of humans under realistic proposed conditions of use is negligible (section 3.6.4).
- if, on the basis of assessment of Community or internationally agreed test guidelines or other available data and information including a review of the scientific literature, it is not considered to have *endocrine disrupting properties that may cause adverse effect in humans* unless the exposure of humans under realistic proposed conditions of use is negligible (section 3.6.5).

During its first reading of the proposed Regulation in November 2007, the European Parliament suggested a number of amendments, including an additional health-based cut-off criterion – that an active substance should only be approved if:

- on the basis of assessment of Community or internationally agreed test guidelines or other available data and information including a review of the scientific literature, it is not considered to cause *a risk of developmental neurotoxic or immunotoxic properties in humans, taking into account exposure during embryonic/foetal life and/or during childhood as well as likely combination effects* unless the exposure of humans under realistic proposed conditions of use is negligible (section 3.6.6).

This annex considers which active substances currently approved for use in plant protection products on the market in the EU, i.e., on Annex I of Directive 91/414/EEC or pending approval, would be affected by the cut-off criteria of CMR1, CMR2 and endocrine disrupting chemicals.

1. CMR 1 & CMR 2

An assessment carried out by the UK Pesticides Safety Directorate in May 2008 considered the impact of the proposed cut-off criteria on the number of active substances that would be available for plant protection purposes and the possible consequences for agricultural production. It did not look at potential health or environmental benefits.

The UK assessment assessed 283 active substances on Annex I or pending approval to see if the cut-off criteria for environmental hazards, e.g., impact on bees, as well as for health hazards would apply. It identified one active substance classified as C1 and R1 (the rat poison warfarin) as well as ten active substances classified as CMR2. A second analysis put forward by four environmental NGOS (EEB, HEAL, PAN Europe, Friends of the Earth Europe) in February 2008 identified warfarin as CR1 as well as nine other active substances classified as CMR 2.

The table below lists the substances identified by the UK Pesticides Safety Directorate as well as by the NGOs. Six of the substances have also been identified as probable endocrine disruptors (ED). It should be noted, however, that in July 2008, four of these substances – which had been pending approval – were in fact not approved or voluntarily withdrawn from the EU market. That leaves only warfarin and seven additional CMR2-classified substances that would be affected by these cut-off criteria.

Active substance	CMR 1 or 2	ED
warfarin	C1,R1	
1-methylcyclopropene	M2	
Bitertanol	R2	ED
Carbendazim	M2,R2	ED
Dinocap	R2	
Fenarimol	R2	ED
Flufenoxuron	C2	
Flumioxazine	R2	
Flusilazole	R2	ED
Glufosinate-ammonium	R2	
Linuron	R2	ED
Procymidone	R2	ED

A search of the PubMed database for epidemiological studies specific to these chemicals identified only one such study for linuron, but quite a few for carbendazim. No epidemiological studies were identified for the other substances.

2. Endocrine disrupters

The UK Pesticides Safety Directorate impact assessment identified 36 active substances that may be considered endocrine disrupters, 30 of which would potentially be taken off the EU market solely on that basis. The NGO analysis identified 17 active substances that may be considered EDs, of which 15 would potentially be taken off the EU market for that reason alone. As the next table shows, 14 of the substances were identified both by the UK PSD study and the NGO analysis; 27 of the substances were identified by the UK alone, and 4 were identified only by the NGOs.

In July 2008, after both studies had been circulated, the regulatory committee of Member State representatives met to take decisions on approval or non-approval of a number of these substances. As a consequence, 25% of these substances (8 out of 32) were not approved and are no longer on the EU market.

EDs identified by both analyses	UK	NGOs	Reg. status
2,4-DB	x		2001/103
2,4-D		x	2003/31
Acetochlor		x	withdrawn
Amitrole	x	x	2001/21
Bifenthrin	x	x	pending
Bromuconazole	x		not approved
Cyproconazole	x	x	withdrawn
Deltamethrin	x	x	2003/5

EDs identified by both analyses	UK	NGOs	Reg. status
Difenoconazole	x		2008/69
Dimethoate	x		2007/25
Epoxiconazole	x	x	approved 7/08
Fenbuconazole	x		not approved
Fluquinconazole	x		not approved
loxynil	x	x	2004/58
Iprodione	x	x	2003/31
Lambda-cyhalothrin		x	2000/80
Mancozeb	x	x	2005/72
Maneb	x	x	2005/72
Metam-sodium		x	pending
Metconazole	x		2006/74
Metiram	x	x	2005/72
Metribuzin	x	x	2007/25
Myclobutanil	x	x	withdrawn
Penconazole	x		pending
Picloram	x	x	2008/69
Prochloraz	x		not approved
Propanil	x		not approved
Propiconazole	x		2003/70
Tebuconazole	x		pending
Tetraconazole	x		pending
Thiram	x	x	2003/81
Triadimenol	x		pending

3. Developmental neurotoxins & immunotoxins

At least 90 active pesticidal substances have been identified as having possible neurotoxic properties (Grandjean and Landrigan, 2006). The table below summarises the regulatory status of these 90 active substances. It is the result of a comparison of these substances with the European Commission's database of 1189 active substances and their regulatory status.

Regulatory status in EU	No. of neurotoxic pesticides
Total on Grandjean/Landrigan list	90
Banned for use	14
Not notified or withdrawn	3
Not approved for Annex I	48
Not found on list of AS	17
Total neurotox AS not used in EU	82
Approved for Annex I	7
Under consideration for approval	1
Total neurotox AS still used in EU	8

As the table shows, 65 of the 90 active substances identified in the Grandjean article are either banned or not approved for use in the EU. Seventeen (17) of the active substances could not be found on the EU database of active pesticidal substances, and most likely are substances never notified under Directive 91/414/EEC. In addition, another substance – nicotine – is currently under consideration for possible inclusion in Annex I of Directive 91/414.

This leaves seven (7) active substances with likely neurotoxic properties that are currently on Annex I of Directive 91/414/EEC, i.e., approved for use in plant protection products on the market in the EU. These substances, which could be affected by the more stringent cut-off criteria are:

Neurotoxicants on Annex I	Identified as ED
Chlorpyrifos	
Cypermethrin	
2,4-D	X
Deltamethrin	X
Dimethoate	X
Ethoprop	
Thiram	X

As the above table indicates, four of these substances have already been identified as possible endocrine disruptors. One of the remaining three AS – chlorpyrifos – has been strongly associated with low birth weight and reduced head circumference following pre-natal exposure (Whyatt et al., 2004).

4. Immunotoxics

The following table lists active substances on Annex I, or whose status on Annex I is pending, that have been associated with immune system effects in humans and/or in experimental animal studies. The list is compiled from a review of the scientific literature and may not be comprehensive. Eight of these 23 active substances also have been identified as endocrine disruptors, and four are considered neurotoxicants. Thus the number of substances previously uncaught by other criteria on this list is 14.

Immunotoxics on Annex I	Identified as ED	Identified as neurotoxicant	Regulatory status
2,4-D	X	X	01/103/EC
Bentazone			00/68/EC
Captan			07/5/EC
Chloridazon			2008/41
Chlormequat			Pending
Chlorpropham			04/20/EC
Chlorpyrifos		X	05/72/EC
Copper sulphate			Pending
Dimethoate	X	X	07/25/EC
Diquat			01/21/EC
Diuron			Voted ScoFCAH 8/08
Mancozeb	X		05/72/EC
Maneb	X		05/72/EC
MCPA			05/57/EC
Metam sodium	X		Pending

Immunotoxicants on Annex I	Identified as ED	Identified as neurotoxicant	Regulatory status
Methiocarb			07/5/EC
Metiram	X		05/72/EC
Metribuzin	X		07/25/EC
Molinate			03/81/EC
Pirimicarb			06/39/EC
Thiram	X	X	03/81/EC
Triallate			Pending
Ziram			03/81/EC

ANNEX III

Other benefits assessments reviewed for this study

Other benefits assessments reviewed for this study

The benefits related to reduced exposure to chemicals and pesticides have been studied through a number of analyses. Most of the analyses have acknowledged the difficulty of accurately identifying the benefits and therefore have made very conservative estimates. This annex summarises the findings of the benefit assessments reviewed for this study.

1. REACH Extended Impact Assessment (European Commission)

This study estimated that the total health benefits from REACH would be in the order of magnitude of €50 billion over the next 30 years (Commission Staff Working Paper (2003)). This figure assumes that 1.0% of all disease (measured in Disability Adjusted Life Years – DALYs) is due to agro-industrial chemicals and chemical pollution from diffuse sources (K. Lvovsky (2001)) and that 90% of any health impacts are either related to historical exposures, will not be identified by REACH or cannot be tackled. This still leaves 45,000 DALYs that can be avoided every year due to REACH. Assuming 10 DALYs are equivalent to 1 life saved (WHO (2002)), then 4,500 lives will be saved due to REACH every year. The value of €1 million per statistical life was used (European Commission (2000)).

2. Assessment of the Impact of the New Chemicals Policy on Occupational Health (RPA)

This study (RPA (2003)) provided an assessment of the potential reduction in occupational health impacts at the EU-15 level from the implementation of REACH. The study concluded that the estimated health impact reductions arising from REACH ranged from around €8 billion to €27 billion for the lower bound assumptions on the number of cases that will be reduced through increased test data and authorisation. For the lower bound figure, it was assumed that only 0.23% of total annual cancers deaths in the EU are associated with exposure to unknown chemical carcinogens in the workplace and thus could potentially be avoided as a result of more data being available on chemical properties through REACH.

One of the main conclusions of the RPA study is that more than 99% of the reduction in occupational health impacts that may arise at EU-15 level from the implementation of the REACH regulation comes from the avoidance of future cancer deaths. The estimated value of reducing skin and respiratory diseases only accounts for approximately €6 million of the total €27 billion benefits expected over a 30 year time period.

3. REACHing the workplace. How workers stand to benefit from the new European policy on chemical agents (ETUC)

The European Trade Union Technical Bureau for Health and Safety (Musu (2004)) estimated the proportion of certain diseases that may indeed be related to exposure to chemicals (see table below). These calculations suggest that at least 4% of occupational cancer cases and 2% of occupational neurological disease cases are related to chemical exposure.

Occupational diseases	% linked to chemicals exposure	% amongst all recognised diseases	% chemicals related amongst all recorded diseases
Cancers	4 – 90% *	5%	0.2 - 4.5% *
Neurological diseases	2 %	8%	0.2 %
Respiratory diseases	36 – 89% *	14%	5.0 – 12.5% *
Skin diseases	88%	14%	12.3%
Total			~ 18% to 30% *

Table x: Estimated percentage of occupational diseases related to exposure to chemical substances.

* including chemical dust (asbestos, silica dusts, wood dusts)

4. The impact of REACH on occupational health with a focus on skin and respiratory diseases (Sheffield University)

This study analysed the impact of the 2003 European Union REACH proposal on the health of the EU-25 workforce (Pickvance S et al (2005)) and calculated the economic benefits due to the reduction in the burden of occupational skin and respiratory diseases under REACH. They assumed all cases of diseases attributable to chemicals were likely to be affected by REACH, unlike the RPA study. The incidence per million per year without REACH for asthma, COPD and dermatitis was estimated at 400, 500 and 400 respectively, of which those potentially preventable by REACH are 50%, 10% and 50%, respectively. Using a working population figure for EU-25 of 200 million, the number of future cases per year that might be avoided thanks to REACH are 40 000 for asthma, 10 000 for COPD and 40 000 for dermatitis.

The costs associated with skin and respiratory diseases are composed of 3 elements: health service costs; productivity costs; and the value of the lost health-related quality of life to the individual. The estimate for cost savings due to REACH, over a 10-year time horizon is estimated to be around €3.5 billion. Over a 30-year time horizon, when the full effects of REACH are in place for the majority of the time period, the aggregate cost savings are estimated to be just over €9 billion.

5. Danish Government Report

A Danish government report (Miljøministeriet (2004)) used RPA estimates of case numbers and cost estimates based on an earlier Danish report (Serup-Hansen N et al (2004)). This report estimated the health benefits for Denmark alone, due to improvements in the working environment, to be worth between €5 million and €737 million over a 30-year period at 2002 prices.