

Abbreviations

For an explanation of many of these terms see the Glossary.

ADI	Acceptable daily intake
BAT	Best available technique
CoT	The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
EAL	Environmental Assessment Level
EPAQS	Expert Panel on Air Quality Standards
FEV1	Forced expiratory volume in 1 second
HSC	Health and Safety Commission
H1	Horizontal guidance note
HSE	Health and Safety Executive
IARC	International Agency for Research on Cancer
IIA	Irritant-induced asthma
IOELV	Indicative occupational exposure limit value
IPC	Integrated pollution control
IPPC	Integrated pollution prevention and control
l	Litre
LC₅₀	Lethal concentration to 50%
LOAEL	Lowest observed adverse effects level
mg	Milligram (one thousandth of a gram)
mg/m³	Milligrams per cubic meter of air
ml	Millilitre (one thousandth of a litre)
NOAEL	No observed adverse effect level
OEL	Occupational exposure limit
PPC	Pollution prevention and control
ppm	Parts per million
RADS	Reactive airways dysfunction syndrome
STP	Standard temperature and pressure
SWORD	Surveillance of Work-Related & Occupational Respiratory Disease
USEPA	United States Environmental Protection Agency
WHO	World Health Organisation

Glossary

Acute toxicity/effects	Adverse effects occurring within a short time of administration of a single dose of a chemical, or immediately following short or continuous exposure, or multiple doses over 24 hours or less.
Allergic rhinitis	Medical term for hay fever. A common allergic reaction that causes inflammation of the nose. Symptoms typically include sneezing, congestion, a runny nose, and an itchy nose.
Alveoli	Tiny sac-like air spaces in the lung where carbon dioxide and oxygen are exchanged.
Antioxidant	A substance that inhibits oxidation, and can guard the body from the damaging effects of free radicals.
Asthma	A disease in which the lung's airways become inflamed and prone to become narrowed in response to provoking stimuli, including allergens and irritating chemicals.
Best available technique (BAT)	The meaning of this term can depend on the context within which it is used. When used in the context of IPPC or PPC it is defined as the most effective and advanced technique for the prevention, or where that is not practicable, the minimisation of emissions and impact on the environment as a whole. It includes consideration of the availability of the technique for the type of process concerned and cost. However, the term BAT may also be applied in the context of the IPC regime where it has a similar meaning to that under IPPC or PPC except that costs are not taken into consideration. See also Integrated Pollution Prevention and Control, Integrated Pollution Control and Pollution Prevention and Control.
Bronchi	The large air passages that lead from the trachea (windpipe) to the lungs.

Broncho-constriction	Constriction of the bronchial airways in the lungs, causing shortness of breath, tightness in the chest, coughing, and wheezing.
Carcinogen	An agent capable of inducing cancer.
Cardiopulmonary	Relating to the heart and lungs.
Cardiovascular	Relating to the heart and blood vessels.
Chemical pneumonitis	An inflammation of the lungs (pneumonitis) or breathing difficulty caused by inhalation of noxious chemicals.
Chronic toxicity/effects	Adverse effects occurring as a result of multiple exposures occurring over an extended period of time, or a significant fraction of the animal's or the individual's lifetime (usually more than 50%).
Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (CoT)	An independent scientific committee that provides advice to the Food Standards Agency, the Department of Health and other Government Departments and Agencies on matters concerning the toxicity of chemicals.
Control group (or reference group)	A group used as the baseline for comparison in epidemiologic studies or laboratory studies. This group is selected because it either lacks the disease of interest (case-control group) or lacks the exposure of concern (cohort study).
Conjunctivitis	Inflammation or infection of the membrane lining the eyelids (conjunctiva).
Corticosteroids	Anti-inflammatory drugs created from or based on a naturally occurring hormone (cortisone) produced by the cortex of the adrenal glands.
Dental fluorosis	A condition that results from excessive fluoride exposure that often causes the teeth to become discolored and the enamel of the teeth to look spotted, pitted, or stained.
Dose-response relationship	The relationship between a quantified exposure (dose), and the proportion of subjects demonstrating specific, biological changes (response).
Dyspepsia	Digestive upset, which can include nausea, vomiting, and heartburn.

Environmental assessment level (EAL)	Benchmarks in a particular environmental media which denote the concentration of a chemical that should have no adverse effects on the natural environment or human health. By comparison with the predicted environmental concentrations arising from releases, they are intended to enable the significance of releases to be assessed, the need for further pathway modelling to be determined and the relative impact of pollutants released to different environmental media to be compared.
Epithelium	The tissue that covers the external surface of the body and lines hollow structures.
Exostosis	An overgrowth of bone which results in a bony projection or spur.
Fibrin	A protein essential for the clotting of blood.
Forced expiratory volume in 1 second (FEV1)	The volume of air that can be expired during the first second of a forced expiration, i.e. during blowing out as hard as possible.
Forced vital capacity (FVC)	The volume of air expired in a forced expiration following maximum inspiration.
Free radical	A molecule containing an unpaired electron, typically highly unstable and reactive. Free radicals can damage the molecular machinery of biological systems, leading to cross-linking and mutation.
Health and Safety Commission (HSC)	The Health and Safety Commission's remit is to protect everyone in Great Britain against risks to health or safety arising out of work activities; to conduct and sponsor research; promote training; provide an information and advisory service; and submit proposals for new or revised regulations and approved codes of practice.
Health and Safety Executive (HSE)	Britain's Health and Safety Commission (HSC) and the Health and Safety Executive (HSE) are responsible for the regulation of almost all the risks to health and safety arising from work activity in Britain.

Horizontal Guidance Note (H1)	The name of the guidance note issued by the Environment Agency which describes how operators should assess the environmental impact of processes and appraise the Best Available Techniques when applying for a permit under the Pollution Prevention and Control (PPC) regime. The term 'Horizontal' refers to the fact that the guidance can be applied across all the sectors covered by PPC.
Hyperplasia	An increase in the number of cells in a tissue or organ, not due to tumour formation.
Hyper-responsiveness	Exaggerated response to a variety of stimuli.
Hypohalous	Compound in which a hydroxyl group (OH) is combined with a halogen atom.
Indicative occupational exposure limit values (IOELVs)	European Community limit values, which are health based and are set under the EU Chemical Agents Directive (98/24/EC) (earlier Directives referred to them as ILVs). They indicate levels of exposure to hazardous substances considered to provide protection from ill health caused by work. IOELVs are similar to the British OELs system under COSHH.
Integrated pollution control (IPC)	Prior to the PPC regulations coming into force, many industrial sectors covered by the IPPC Directive were regulated under Part I of the Environmental Protection Act 1990. This introduced the systems of Integrated Pollution Control (IPC), which controlled releases to all environmental media, and Local Air Pollution Control (LAPC), that controlled releases to air only. Processes regulated under IPC were controlled by the Environment Agency in England and Wales and were potentially the most polluting or technically complex. LAPC was operated by local authorities. Similar but separate arrangements were applied to Scotland and Northern Ireland. The objective of IPC was to use the Best Available Techniques Not Entailing Excessive Cost (BATNEEC) to prevent releases or where that was not practicable to minimise and render them harmless.

Integrated pollution prevention and control (IPPC)

The system of Integrated Pollution Prevention and Control (IPPC) applies an integrated environmental approach to the regulation of certain industrial activities. This means that emissions to air, water (including discharges to sewer) and land, plus a range of other environmental effects, must be considered together. It also means that regulators must set permit conditions so as to achieve a high level of protection for the environment as a whole. These conditions are based on the use of the Best Available Techniques (BAT), which balances the costs to the operator against the benefits to the environment. IPPC aims to prevent emissions and waste production and where that is not practicable, reduce them to acceptable levels. IPPC also takes the integrated approach beyond the initial task of permitting, through to the restoration of sites when industrial activities cease. IPPC was introduced by the European Community (EC) Directive 96/61/EC on Integrated Pollution Prevention and Control (the IPPC Directive). The Directive is implemented by the Pollution Prevention and Control (England and Wales) Regulations 2000, SI 2000/1973. Separate systems have been introduced to apply the IPPC Directive to Scotland, Northern Ireland and the offshore oil and gas industries. Industrial activities are being brought under the control of the regulations on a sector by sector basis according to a timetable set out in the regulations and the Directive will not be fully implemented until 2007. See also Pollution Prevention and Control and Integrated Pollution Control.

Lacrymation

The production of excess tears; crying.

Laryngeal

Having to do with the larynx (voice box).

LC₅₀

LC₅₀ is that concentration lethal to 50% of those exposed for the stated time.

Metabolic acidosis

A condition in which the blood is too acidic.

Methacholine challenge

A type of bronchial challenge or inhalational challenge used as a test for airway reactivity or atopic asthma; aerosolised methacholine is applied to the airways and the patient is assessed for responsiveness or hyper-responsiveness.

Mucous membranes	The moist membrane lining all body passages that communicate with the air, such as the nasal sinuses and respiratory and alimentary tracts, and having cells and associated glands that secrete mucus. Also called <i>mucosa</i> .
Mucosa	See mucous membranes.
Nasal	Of the nose.
Nasal lavage	Washing from the nose by repeated injections with a solution.
Neural	Having to do with nerves or the nervous system.
Neutrophil	A type of white blood cell that is active in immune responses and inflammatory reactions.
No observed adverse effect level (NOAEL)	A highest exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse, nor precursors to adverse effects. (Sometimes referred to as no observed adverse effect concentration (NOAEC)).
Occupational Exposure Limit (OEL)	The UK Health and Safety Commission (HSC) sets occupational exposure limits (OELs) which are concentrations of substances in the air at or below which occupational exposure is considered to be adequate.
Oedema	Excessive accumulation of fluid in the body tissues When fluid accumulates in the lungs, this is known as a pulmonary oedema.
Ossification	Process by which bone is formed.
Osteosclerosis	Abnormal hardening or increased density of bone.
Pharmacokinetic	Referring to the absorption, distribution, metabolism and excretion of a drug.
Plasma	The liquid part of the blood in which the red blood cells, the white blood cells, and platelets are suspended.
Pneumonitis	An inflammation of the lungs.

Pollution Prevention and Control (PPC)	The Pollution Prevention and Control (England and Wales) Regulations 2000, SI 2000/1973 implement the requirements of the European Community (EC) Directive 96/61/EC on Integrated Pollution Prevention and Control (the IPPC Directive), in so far as it relates to installations in England and Wales. Separate systems have been introduced to apply the IPPC Directive to Scotland, Northern Ireland and the offshore oil and gas industries. The regulatory regime established by the regulations is often known as the PPC regime. See also Integrated Pollution Prevention and Control and Integrated Pollution Control.
ppm	Parts per million.
Pulmonary	Relating to the lung.
Pulmonary oedema	Build up of fluid in the lungs which causes breathlessness.
Respiratory airway resistance	The resistance of the airways to airflow through them. Measured in some animal experiments and occasionally in man.
Respiratory tract	The organs that are involved in breathing. These include the nose, throat, larynx, trachea, bronchi, and lungs. Also known as the respiratory system.
Respiratory mucosa	The moist membrane lining the organs involved in breathing including the nose, throat, larynx, trachea, bronchi, and lungs.
Rhinitis	Inflammation of the lining of the nose.
Safety factor	A number (equal or greater than 1) used to divide NOAEL or LOAEL values derived from measurements in animals or small groups of humans, in order to estimate a NOAEL or LOAEL value for the whole human population; also called uncertainty factor. Safety factors are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to humans, (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure, (4) the uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) the uncertainty associated with extrapolation from animal data when the data base is incomplete.

SHEILD	Midland Thoracic Society's Surveillance Scheme for Occupational Asthma for the West Midlands.
Skeletal fluorosis	An excessive accumulation of fluoride in bone associated with increased bone density and outgrowths.
Squamous cell metaplasia	A change in the nature of tissue into squamous epithelium; may be an early sign of malignant change.
Squamous cell	An epithelial cell that is flat like a plate and forms a single layer of epithelial tissue (tissue that covers the external surface of the body and lines hollow structures).
Subacute toxicity/effects	See subchronic toxicity/effects.
Subchronic toxicity/effects	Between acute and chronic toxicity, also called subacute toxicity. Adverse effects occurring as a result of repeated daily dosing of a chemical, or exposure to the chemical, for part of an organism's lifespan (usually not exceeding 10%). With experimental animals, the period of exposure may range from a few days to 6 months.
Surfactant	A substance formed in the lungs that helps keep the small air sacs, or alveoli, from collapsing and sticking together.
Surveillance of Work-Related & Occupational Respiratory Disease (SWORD)	Scheme that aims to determine the scale and patterns of work-related respiratory disease in the UK and to identify the agents thought to be responsible along with information on industry and occupation. It has been running since 1988 and is funded by the Health and Safety Executive, with the support of the British Thoracic Society and the Society of Occupational Medicine. Approximately 450 respiratory physicians throughout the UK participate in reporting occupational respiratory disease. Twenty of these are core reporters who report every month; the remainder are sample reporters who are sampled at random and report for one month only each year.
Susceptible group	A group of people who, as a result of genetic predisposition, age, illness or unusual exposure, are more affected by toxic substances than other people (See Section 1.2.2 and Appendix 1 for more detail).

Systemic effect	Concerning or affecting the body as a whole.
Threshold Limit Values (TLVs)	These values are established by the American Conference of Governmental Industrial Hygienists (ACGIH). They are the concentration in air of a substance to which, it is believed that, most workers can be exposed daily without adverse effect. Quoted as time weighted concentrations for a 7 or 8 hour workday and a 40 hour working week. For most substances the value may be exceeded, to a certain extent, provided there are compensating periods of exposure below the value during the workday, or in some cases working week. A limited number of substances are given ceiling concentrations that should never be exceeded.
Time-weighted average	The average concentration of a chemical to which it is permissible to expose a person to over a given time period.
Tracheobronchitis	Common respiratory infection characterised by inflammation of the trachea (windpipe) and the bronchi (tubes that carry air from the trachea to the lungs).
Upper respiratory tract	Includes the nose, sinuses, pharynx (throat), and larynx (voice box). The lower respiratory tract includes the trachea (windpipe), bronchial tubes (two branches from the windpipe), bronchioles (smaller bronchial tubes), and alveoli (tiny sacs in the lungs where the exchange of oxygen and carbon dioxide occurs).
Uric acid	Product of protein metabolism (breakdown).
WATCH Panel	Health and Safety Commission's Advisory Committee on Toxic Substances.

Appendix 1: Children as a vulnerable group

A1.1: Background

167. In 1997, the environmental ministers of the G8 signed a declaration that national policies should take into account the specific exposure pathways and dose-response characteristics of children when conducting risk assessment and setting protective standards. When considering the effect of breathing halide gases, EPAQS considered the factors that could increase the vulnerability of children to these agents.

A1.2: Lung growth and physiology

168. From birth to 8 years of age, the lung grows by developing new breathing units (i.e., new alveoli and capillaries). Thereafter, lung growth is maintained through expansion of these structures (Dietert *et al.*, 2000). At birth, the surface area of the lung is 3 m², which increases in proportion to the rest of the body to 75 m² in adulthood (Clewell *et al.*, 2002). Since changes in lung surface area closely match overall body growth (e.g., weight), exposure of the lower airway to inhaled gases per breath is approximately the same in children and adults. However, the metabolic rate of children is significantly higher than in adults. In order to match oxygen consumption with carbon dioxide production, children must breathe more frequently than adults. This, in turn, results in an increased exposure per minute of the lower airways of children to inhaled gases (de Zwart *et al.*, 2004). Thus the volume of inhaled air indexed to body weight (a marker of lung surface area) is 400 ml/minute/kg for newborns (Figure 1) and 150 ml/minute/kg for adults (Etzel & Balk, 2003).
169. Over the longer-term, inhaled toxins that deviate the normal pattern of lung growth may impair lung function in adulthood. For example, Gauderman recently reported that children exposed to a combination of high levels of nitrogen dioxide, acid vapour and particulate matter over an eight year period showed deficits in growth in their forced expiratory volume in one second (FEV1) (Gauderman *et al.*, 2004). Although it is not clear whether these changes are permanent or reversible, these data suggest that long-term exposure to pollutants from fossil fuels may affect lung growth.

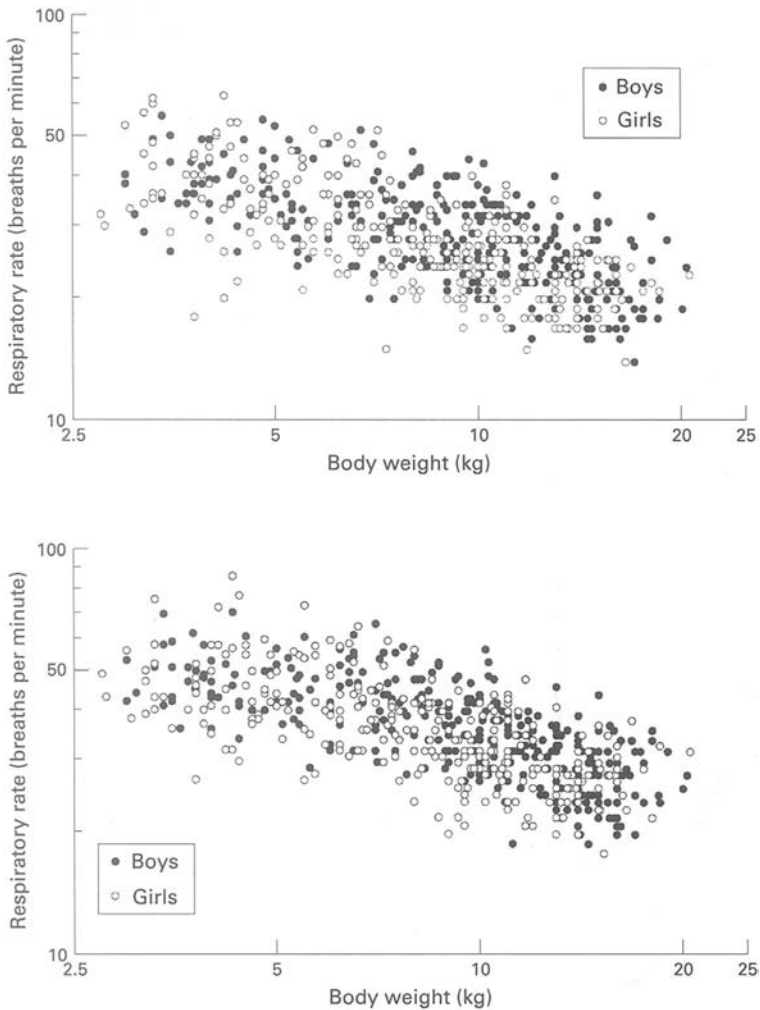


Figure 1. Relationship between respiratory rate and body weight. (Source: Gagliardi & Rusconi, 1997).

A1.3: Lung defences

170. Many respiratory pollutants are powerful oxidants and their impact relates in part to the ability of the lung to nullify the oxidant challenge (Kelly, 2003). The mature lung has a range of antioxidant defences, which together perform this task. Prior to birth, pulmonary (lung) antioxidant defences, like the surfactant system, are immature. This developmental pattern is highlighted in babies born prematurely and who require supplemental oxygen – resulting in oxidative lung injury (Schock *et al.*, 2001). It is unclear whether the lung antioxidant defences in children are better, worse or the same as adults.

A1.4: Models of exposure

171. Models have been developed that compare the effects of irritant gases in adults and children (Sarangapani *et al.*, 2003). Table 1 shows the effect of age on the modelled exposure of lower respiratory tract cells for ozone (an irritant and oxidising gas). There is little difference in exposure between males and females, but for the same inhaled concentration, infants and children have increased exposure compared with adults.

Table 1. Effect of age and gender on extraction of ozone by lower airway cells, indexed to a 25-year-old. (Adapted from Sarangapani *et al.*, 2003).

Age (years)	Extraction of ozone per unit surface area of airway	
	Male	Female
1	4.5	6.6
5	1.9	2.8
10	1.8	2.4
15	1.4	1.6
25	1.0	1.0

A1.5: Summary

172. There are factors that could increase the vulnerability of children's lungs to irritant gases. However, it remains uncertain whether children are a vulnerable group when considering the effects of halide gases. We have therefore taken a precautionary approach, and have explicitly considered children as a “potentially” vulnerable group. A correction factor has therefore been applied to take this uncertainty into account.

References

- Clewell, H.J., Teeguarden, J., McDonald, T., Sarangapani, R., Lawrence, G., Covington, T. (2002). Review and evaluation of the potential impact of age- and gender-specific pharmacokinetic differences on tissue dosimetry. *Crit. Rev. Toxicol.* **32**, 329–389.
- Dietert, R.R., Etzel, R.A., Chen, D., Halonen, M., Holladay, S.D., Jarabek, A.M. (2000). Workshop to identify critical windows of exposure for children's health: immune and respiratory systems work group summary. *Environ. Health Perspect.* **108**, Suppl. 3, 483–490.
- Etzel, R.A. & Balk, S.J. (eds) (2003). Developmental toxicity: special considerations based on age and developmental stage. In: *Pediatric Environmental Health*. pp 9–23. American Academy of Pediatrics, Elk Grove Village, IL, USA.

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Gagliardi, L., Rusconi, F. (1997). Respiratory rate and body mass in the first three years of life. The working party on respiratory rate. *Arch. Dis. Child*; 76, 151-4.

Gauderman, W.J. *et al.* (2004) The effect of air pollution on lung development from 10 to 18 years of age. *N. Engl. J. Med.* **351**,1057–1067.

Kelly, F.J. (2003). Oxidative stress: its role in air pollution and adverse health effects. *Occup Environ Med.* **60** (8), 612-6.

Sarangapani, R., Gentry, P.R., Covington, T.R., Teeguarden, J.G., Clewell, H.J. (2003). Evaluation of the potential impact of age- and gender-specific lung morphology and ventilation rate on the dosimetry of vapors. *Inhal. Toxicol.* **15**, 987–1016.

Schock, B.C. *et al.* (2001). Oxidative stress in lavage fluid of preterm infants at risk of chronic lung disease. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **281**, 1386–1391.

de Zwart, L.L., Haenen, H.E., Versantvoort, C.H., Wolterink, G., van Engelen, J.G., Sips, A.J. (2004). Role of biokinetics in risk assessment of drugs and chemicals in children. *Regul. Toxicol. Pharmacol.* **39**, 282–309.

Appendix 2: Irritant-induced asthma and RADS

Note that this appendix, which was originally published on the internet at <http://www.defra.gov.uk/environment/airquality/aqs/pdf/rads.pdf>, was commissioned to inform EPAQS about the general issues associated with irritancy. It is not specific to halogens and hydrogen halides.

A2.1: Summary

173. A single high exposure of a person to an irritant chemical by inhalation, typically as an accidental incident involving a gas or vapour, can mean they run the risk of developing a type of asthma called reactive airways dysfunction syndrome or RADS. These people have irritable bronchial tubes and this hypersensitive state may last for some years. In many cases (although not all) it is much more resistant to treatment than conventional asthma but is a relatively rare condition; fewer than one in a thousand of all cases of asthma starting in adulthood are RADS. The condition has not been reported in children.
174. More recently, it has been suggested that lower levels of exposure to irritant substances repeatedly over time may also lead to the development of asthma. As it is possible that the biological processes involved in these people are similar to those seen in RADS, the general term irritant induced asthma (IIA) has been applied to this condition, a term which now includes RADS itself. Little is known of the outcome for IIA in general, but it is unlikely that it differs substantially from that in conventional asthma. Although outdoor air contains substances which, at high dose, have been known to cause RADS, levels of exposure to the population breathing outside air on a day-to-day basis are very much lower than those which would result in RADS. Consequently, although in theory persistent exposure to low levels of substances which at high dose can cause RADS could themselves lead to the development of asthma, it is most unlikely that this occurs in the population at large.

A2.2: Terminology and definition

175. The term, reactive airways dysfunction syndrome (RADS) was first coined by Brooks in 1985 (Brooks *et al.*, 1985) when he produced fairly

strict criteria for an asthmatic-like state occurring within 24 hours of an acute, very high dose exposure and the presence of bronchial hyper-responsiveness to methacholine. In 1995 a consensus statement on asthma in the workplace (Chan-Yeung, 1995) suggested that these strict criteria should be relaxed slightly and a more comprehensive term introduced, namely irritant induced asthma (IIA). The criteria for IIA were laid down as:

- absence of previous respiratory complaints;
- onset of asthma symptoms within 24 hours of a single exposure to a high concentration of respiratory irritant gas;
- persistence of asthma symptoms for at least 3 months after exposure;
- symptoms associated with increased bronchial responsiveness and/or the presence of airflow obstruction with reversibility to bronchodilator in the absence of previous lung disease.

176. This definition would cover all forms of IIA, including classical RADS and low-dose exposure to irritants over time. This issue of a changing definition was highlighted in a recent review of the area (Tarlo, 2003), where it was recognised that some authors included multiple acute exposures as causing IIA, some allowed up to a week after exposure for the onset of symptoms to occur, and some allowed lesser degrees of exposure – so called low-dose RADS or “not so sudden IIA” in their definition of IIA (Brooks *et al.*, 1998). The possibility of exposures such as those which are recognised to lead to RADS/IIA could cause a stepwise worsening of patients with pre-existing respiratory disease is plausible but does not fall under these definitions. However, in the context of considering the health effect of the specific ambient exposures considered here, this should be regarded as possible although difficult to prove.
177. This raises the issue of non-peak irritant exposures to gases, fumes and some dusts as a cause of airways disease but, while the causal pathways may be real, the evidence is based on isolated reports or small series. However, this concept fits with reports of asthma developing in cleaners and workers chronically exposed to solvents (Medina-Ramon *et al.*, 2003; Rosenman *et al.*, 2003) and is consistent with the finding that 18% of cases of occupational asthma reported to the SHIELD Scheme in the West Midlands were due to irritants (Gannon & Burge, 1993). More recently a European survey (Kogevinas *et al.*, 1999) also showed similar associations in workers exposed to irritants. In the occupational setting, small but above normal exposures have been reported to result in accelerated fall in forced expiratory volume in one second (FEV1) and enhanced bronchial responsiveness (Gautrin *et al.*, 1999).
178. If accepted, this variation in the diagnostic criteria for IIA will lead to differences in assessment of its prevalence. Estimates depending upon the diagnostic criteria used, range from 2-3% (Brooks *et al.*, 1985; Tarlo & Broder, 1989) up to 18% (Ross & MacDonald, 1996).
179. From the point of view of environmental exposures, the possibility that longer-term exposures to chemicals might lead to asthma is therefore of

great relevance when deciding about air quality standards. However, there are no usable data to aid our deliberations in this regard.

180. The SWORD database has had 301 cases of halide exposure resulting in respiratory disease reported to them, with an estimate of the likely total UK number being 477 between 1989 and 2003. Using the estimated UK figures, 338 were due to chlorine, 130 to hydrogen chloride (either as gas or acid) and 9 to bromine. Most were recorded simply as inhalation accidents (with presumably no medium- to long-term sequelae) but 69 (20%) of those exposed to chlorine were reported to have developed asthma (whether irritant or sensitised) as did 26 (20%) of those exposed to hydrogen chloride. The commonest occupational group exposed was chemical, gas and petroleum operators (10% for chlorine, 8.5% for hydrogen chloride). This implies that a substantial minority of those exposed to either of these agents in an acute high dose develop an asthma type syndrome as a result, but these exposures are generally assumed to be far higher than any ambient exposures other than those encountered as spills/leaks.

A2.3: Pathology

181. There is very little difference if any between the histological appearances of IIA/RADS and conventional occupational asthma. There is some suggestion that in RADS there is less airway eosinophilic infiltration and more fibrosis (Brooks *et al.*, 1985) but data are very limited.
182. It is possible that specific exposures may lead to reproducible patterns of IIA, such as exposures to chlorine (Chan-Yeung *et al.*, 1994; Gautrin *et al.*, 1994). In one such worker (Lemiere *et al.*, 1997) who underwent bronchial biopsies on four occasions, initial epithelial desquamation with fibrinous exudate was followed by proliferation of basal cells and regeneration of the epithelium leading to collagen deposition in the submucosa with basement membrane thickening (Boulet *et al.*, 1997) which might explain the attenuated airflow limitation reversibility seen in RADS. These steps were confirmed in animal models (Demnati *et al.*, 1998) but, interestingly, inflammatory cells do not seem to play an essential role. However, this proposed model is not consistently supported in larger studies (Glindmeyer *et al.*, 1997).
183. The association of what appears to be IIA in rescue workers involved in the destruction of the World Trade Centre (Prezant *et al.*, 2002) suggests that this condition merely represents the final common pathway of a number of patterns of insults resulting in persistent airway irritative symptoms but with no specific underlying pathology.

A2.4: Risk Factors

184. Specific risk factors may contribute to the development of IIA. The most important causal factor is the dose of the agent as the nearer

individuals are to a spill, the greater is the risk of developing RADS (Jajosky *et al.*, 1999; Renisch *et al.*, 2001). Current cigarette smoking and atopy also appear to be risk factors although less strongly than has been identified for conventional occupational asthma.

A2.5: Prognosis

185. In classical RADS, the tendency is for improvement to occur over time, although in many individuals symptoms continue for years. There is much less evidence about what happens with IIA more broadly although the implication is that this is a much more permanent state of affairs. However, as yet, there are no longitudinal studies in these particular groups.
186. In one follow up study (Malo *et al.*, 1994), normalisation of FEV1 and PC₂₀⁷ to methacholine in approximately 25% of subjects after two and a half years was seen, the time course of recovery being similar to occupational asthma with a latency period, the maximum improvement occurring in the first two years.
187. Treatment is based on conventional asthma therapy but the response is often poor raising the issue of whether this should be regarded as more of a chronic obstructive pulmonary disease (COPD)/bronchitic picture rather than asthma. There is very limited information on treatment of the condition, the role of oral steroids being debatable although apparently conferring some protection in a mouse model (Das *et al.*, 1993).

A2.6: Summary

188. In summary, IIA is probably commoner than has been thought; is associated with acute high exposures to irritant substances (not just gases); and has a variable prognosis, with some people being disabled for some years after exposure. In general terms, the response to anti-asthma therapy is disappointing.
189. Longer-term exposure to lower levels of irritants may also lead to the development not only of asthma but a COPD/bronchitis picture in exposed workforces (Balmes, 2002). The inference of this observation is that environmental exposures, at an appropriate level, might also be contributing to the development of airways disease in the community. However, the data on dosing is very limited and at this stage it would probably be unwise to infer that ambient (i.e. low-level) exposures to gases or fumes which at high level are known to cause RADS, might contribute to the burden of airways disease.

⁷ Provocation concentration 20: the dose of a test compound which causes a 20% fall in FEV1.

References

- Balmes, J. (2002). Occupational airways disease from chronic low-level exposures to irritants. *Clinics in Chest Medicine* **23**, 727-35.
- Boulet, L.P., Laviolette, M., Turcotte, H., Cartier, A., Dugas, M., Malo, J.L., Boutet, M. (1997). Bronchial subepithelial fibrosis correlates with airway responsiveness to methacholine. *Chest*; **112**, 45-52.
- Brooks, S.M., Weiss, M.A., Bernstein, I.L. (1985). Reactive airways dysfunction syndrome (RADS): persistent asthma syndrome after high level irritant exposures. *Chest*. **88**, 376-84.
- Brooks, S.M., Hammad, Y., Richards, I. (1998). The spectrum of irritant-induced asthma: sudden and not-so sudden and the role of allergy. *Chest* **113**, 42-9.
- Chan-Yeung, M., Lam, S., Kennedy, S., Frew, A.J. (1994). Persistent asthma after repeated exposure to high concentrations of gases in pulp mills. *Am J Respir Crit Care Med*. **149**,1676-80.
- Chan-Yeung, M. (1995). ACCP Consensus Statement on Assessment of Asthma in the Workplace. *Chest*. **108**, 1084-113.
- Das, R., Blanc, P.D. (1993). Chlorine gas exposure and the lung: a review. *Toxicol. Indust. Health*. **9**, 439-55.
- Demnati, R., Fraser, R., Ghezzi, H., Martin, J.G., Plaa, G., Malo, J.L. (1998). Time-course of functional and pathological changes after a single high acute inhalation of chlorine in rats. *Eur. Respir. J*. **11**, 922-8.
- Gannon, P.F., Burge, P.S. (1993). The SHIELD scheme in the West Midlands Region, United Kingdom. *Br. J. Ind. Med*. **50**, 791-6.
- Gautrin, D., Boulet, L.P., Boutet, M., Dugas, M., Bherer, L. *et al.* (1994). Is reactive airways dysfunction syndrome a variant of occupational asthma? *J. Allergy Clin. Immunol*. **93**, 12-22.
- Gautrin, D., Leroyer, C., Infante-Rivard, C., Ghezzi, H., Dufour, J.G., Girard, D., Malo, J.L. (1999). Longitudinal assessment of airway caliber and responsiveness in workers exposed to chlorine. *Am. J. Respir. Crit. Care Med*. **160**, 1232-7.
- Glindmeyer, H., Lefante, J., Freyder, L., Jones, R., Freidman, M., Weill, H. (1997). Relative rate of new onset asthma among workers exposed to irritant chemicals. *Am. J. Respir. Crit. Care Med*. **155**, A258.
- Jajosky, R.A., Harrison, R., Flattery, J. *et al.* (1999). Surveillance of work-related asthma in selected U.S. States - California, Massachusetts, Michigan, and New Jersey, 1993-1995. *MMWR Surveill. Summ*. **48(3)**, 1-20.

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Kogevinas, M., Anto, J.M., Sunyer, J., Tobias, A., Kromhout, H., Burney, P. (1999). Occupational asthma in Europe and other industrialised areas: a population-based study. European Community Respiratory Health Survey Study Group. *Lancet*. **353**, 1750-4.

Lemière, C., Malo, J.L., Boutet, M. (1997). Reactive airways dysfunction syndrome due to chlorine: sequential bronchial biopsies and functional assessment. *Eur. Respir. J.* **10**, 241-4.

Malo, J.L., Cartier, A., Boulet, L.P., L'Archevêque, J., Saint-Denis, F., Bhérier, L., Courteau, J.P. (1994). Bronchial hyperresponsiveness can improve while spirometry plateaus two to three years after repeated exposure to chlorine causing respiratory symptoms. *Am. J. Respir. Crit. Care Med.* **150**, 1142-5.

Medina-Ramon, M., Zock, J.P., Kogevinas, M. *et al.* (2003). Asthma symptoms in women employed in domestic cleaning: a community based study. *Thorax* **58**, 950-4.

Prezant, D.J., Weiden, M., Banauch, G.I., McGuinness, G., Rom, W.N. *et al.* (2002). Cough and bronchial responsiveness in firefighters at the World Trade Center site. *N. Engl. J. Med.* **347**, 806-15.

Renisch, F., Harrison, R.J., Cussler, S. *et al.* (2001). Physician reports of work-related asthma, 1993-1996. *Am. J. Ind. Med.* **39**, 72-83.

Rosenman, K.D., Reilly, M.J., Schill, D.P. *et al.* (2003). Cleaning products and work-related asthma. *J. Occup. Environ. Med.* **45**, 556-63.

Ross, D.J., McDonald, J.C. (1996). Asthma following inhalation accidents reported to the SWORD project. *Ann. Occup. Hyg.* **40**, 645-50.

Tarlo, S.M., Broder, I. (1989). Irritant-induced occupational asthma. *Chest*. **96**, 297-300.

Tarlo, S.M. (2003). Workplace irritant exposures: do they produce true occupational asthma? *Ann. Allergy Asthma Immunol.* **90(suppl)**, 19-23.

Appendix 3: Respondents to Guidelines for Halogens and Hydrogen Halides in Ambient Air for Protecting Human Health against Acute Irritancy Effects – Draft for comment

Comments were gratefully received from the following organisations and individuals on the draft of this report, which was published in April 2005.

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