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Consultation on Addendum to Guidelines for halogen and hydrogen halides in ambient air for protecting human health against acute irritancy effects

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Expert Panel on Air Quality Standards

Addendum to Guidelines for Halogens and Hydrogen Halides in Ambient Air

Provisional Guidelines for Hydrogen Iodide and Hydrogen Fluoride for Protecting Human Health against Chronic Systemic Effects

Contents

Terms of Reference

The Expert Panel on Air Quality Standards (EPAQS) was established in 1991. The terms of reference of the Panel are:

"**To advise** the Secretary of State for Environment, Food and Rural Affairs, Scottish Ministers, the National Assembly for Wales and the Department of the Environment (Northern Ireland) as required, on non-occupational ambient air quality standards, with particular reference to the levels of airborne pollutants at which no or minimal effects on human health are likely to occur;

i. taking account of the best available evidence of the effects of air pollution on human health and of progressive development of the air quality monitoring network; but

ii. without reference to the practicality of abatement or mitigation measures, the economic costs and economic benefits of pollution control measures or other factors pertinent to the management rather than the assessment of risk;

Where appropriate, for example for pollutants where no threshold for adverse effects can be determined, the Panel may wish to recommend exposure-response relationships or other information Government might use to set policy objectives.

to identify gaps in the knowledge needed for standard setting and suggest potential priority areas for future research;

to advise on other aspects of air quality and air pollution referred to it;

for the purpose of informing the development of policy on the improvement of air quality and increasing public knowledge and understanding of air quality issues."

EPAQS does not give approval for products or equipment.

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1 Introduction

1.1 Background to the addendum

1. The Expert Panel on Air Quality Standards (EPAQS) report "*Guidelines for Halogens and Halides in Ambient Air for Protecting Human Health Against Acute Irritancy Effects*" was published in February 2006. These recommended guideline values are intended to represent a level at which no significant health effects would be expected to occur over the short-term, specifically guarding against the effects of acute irritancy. These guideline values are intended for use by the Environment Agency and the Scottish Environment Protection Agency (SEPA) when considering emissions from specific point sources which fall under their regulatory remit. They are not intended for use in setting national air quality standards or objectives.

2. During the development of these guideline values, it was concluded that "*for hydrogen fluoride and hydrogen iodide health effects resulting from longer-term exposure cannot be ruled out*." It was agreed that EPAQS should produce an addendum to its report addressing the long-term (chronic) exposure effects of these specific airborne pollutants, and, if necessary, recommending further values. Once again, these would be intended for use by the Environment Agency and SEPA when considering emissions from specific point sources which fall under their regulatory remit.

3. This addendum proposes *provisional guideline values* for chronic systemic effects resulting from airborne exposure to hydrogen iodide and hydrogen fluoride. It should be read in conjunction with the main report, in particular with reference to the methodology used by EPAQS for recommending guideline values. The same methodology has been used in proposing these provisional guideline values. However, in this case the Environment Agency did not provide EPAQS with a peer reviewed dossier, and the background material for the addendum was sourced by EPAQS and its Secretariat.

4. It should be noted that the provisional guideline values in this report were derived from a very small dataset, based on studies which were, in the main, intended for other purposes or other exposure modes. The level of uncertainty in the provisional values is therefore high, and this was reflected in the application of suitable uncertainty factors. It is intended that the provisional guidelines will be revisited at some point in the future, but this is dependant on an improvement to the current dataset. *EPAQS strongly recommends that further high quality research and monitoring into the chronic effects of inhaled halogens and hydrogen halides is undertaken, with a view to improving the current low level of available data.*

5. It should also be noted that the provisional guideline values reflect only impacts on human health, and excludes impacts on both animal health and ecosystem damage. Hydrogen fluoride in particular is highly phytotoxic, and damage to plants is likely to occur at concentrations

below that proposed for the provisional guideline value. Nevertheless, the terms of reference of EPAQS are clear in restricting the Panel to the consideration of the human health effects of airborne pollutants.

2 Hydrogen fluoride

6. In their main report, the Panel recommended that a concentration of hydrogen fluoride gas or mass equivalent aerosol not exceeding 0.2 ppm (0.16 mg/m^3) over a 1-hour averaging period should protect against irritant and inflammatory effects on the eyes, skin and breathing airways.

2.1 Background

7. The difficulty that EPAQS has found in setting a guideline value for irritancy for hydrogen fluoride is that even at this low level the amount of fluoride inhaled by the lungs could be sufficient to double the average intake of fluoride in adults and also add significantly to the intake in children. Excess fluoride intake from drinking water or other sources is associated around the world with principally two conditions, skeletal fluorosis and dental fluorosis, but concerns have also been raised about the role of fluoride in other disorders, which will be mentioned below.

8. The World Health Organisation (WHO) guideline value for drinking water of 1.5 mg/L was set in 1984 and was last reviewed in 1996, when it was not changed (WHO/IPCS, 2002). This value is higher than that recommended for fluoridation of water supplies (about 1 mg/L in temperate climes). Estimates of total daily fluoride intake vary significantly, depending upon the diet, but can range from below 0.9 mg/day in areas where the water is not fluoridated to about 3 mg/day where the water is fluoridated.

9. In the UK fluoridated areas, drinking water probably remains the most important source of fluoride intake. Up until the 1960s it represented the bulk of fluoride exposure for both adults and children in most populations, but since then the availability of fluoride from other sources, such as toothpastes and dentifrices, means that fluoride in drinking water is just one component of an individual's total fluoride intake (Warren and Levy, 1999).

10. In the early 1990s public health approaches were introduced to limit the exposure to systemic fluoride from toothpaste and supplements.

11. A large epidemiological literature exists on the health effects of water fluoridation. Two useful summaries of the evidence are found in NHS CRD (2000) and MRC (2002). The EPAQS has drawn upon these reviews when considering the health consequences of exposure to hydrogen fluoride as a source of fluoride intake. Further information in relation to recommended dietary intakes in children and adults was available in WHO/IPCS (2002) and EFSA (2005).

2.2 Health effects

2.2.1 Dental fluorosis

12. Even at a low fluoride intake from water, a certain level of dental fluorosis of permanent teeth will be found arising from exposure during

dental enamel formation and tooth development in the early years of life. Enamel fluorosis (mottled teeth) is a hypo-mineralization of enamel, characterised by greater surface and subsurface porosity than normal enamel, and is related to fluoride ingestion during periods of tooth development by young children (during the first six years of life for most permanent teeth). Milder forms are not noticeable, but more severe forms might be objectionable on aesthetic or cosmetic grounds (e.g., CDC, 2005). Historically, a low prevalence of the milder forms of fluorosis has been accepted as a "reasonable and minor consequence" balanced against the substantial protection from dental caries afforded by the use of fluoridated drinking water, dietary fluoride supplements and oral care products.

2.2.2 Skeletal fluorosis

13. Skeletal fluorosis is not normally encountered in the UK, but it is prevalent in certain parts of Africa and India, for example, where fluoride intakes from drinking water are elevated due to a raised fluoride in geological strata that contaminate groundwater, or in China, where the indoor burning of fluoride rich coal (with exposure to hydrogen fluoride) also contributes to high overall fluoride intakes (WHO/IPCS 2002). Bone deposition of fluoride occurs to the extent of 50% in growing children, but only 10% in adults (WHO, 2000). The condition can develop in young children, or after many years of living in an endemic area, but affected bones may manifest as marked limb and spinal deformities which become disabling or very painful.

14. The WHO/IPCS (2002) review on fluorides states that there is evidence suggestive of an increased risk of bone effects at total intakes above about 6 mg fluoride per day, whilst there is clear evidence from India and China that skeletal fluorosis occurs at a total intake of more than 14 mg fluoride per day. However, the epidemiological data are inadequate for drawing a dose–response relation between daily intake and the degree of bone abnormality.

2.2.3 Other health outcomes

15. There are several other health outcomes to consider in relation to water fluoridation. The most important in public health terms is an effect on the risk of hip fracture – studies of fluoride treatment for osteoporosis have found an increased risk of fractures. Studies of individuals undergoing fluoride treatment for osteoporosis, epidemiological studies of communities with naturally high levels of fluoride in drinking water and community based studies of populations with fluoridated water supplies have examined the possible relationship between exposure to fluoride and alterations in bone mineral density and/or the risk of bone fractures. The MRC (2002) report concluded that a small increase (or decrease) in risk cannot be ruled out. Other concerns of an effect include cancer, the immune system, reproductive and developmental defects, and the kidney and the gastro-intestinal tract, but no links with water fluoridation have been established (MRC, 2002). Nonetheless, an updated analysis

of UK data on fluoridation and cancer rates has been recommended (MRC, 2002).

2.3 Sources of fluoride exposure and uptake

2.3.1 General sources

16. There is general agreement in the literature that the main sources of fluoride intake are in the food and water, and fluoride-containing dental products. Daily intake of fluoride varies widely. The intake from tap water, especially by children, is commonly grossly over-estimated. Beverages can be a significant source of fluoride intake in children. Some sub-groups in the population may be exposed to levels of dietary intake of fluoride considerably higher than the mean estimates. The bioavailability of ingested fluoride is also important and remains poorly understood (MRC, 2002).

17. A number of studies, using a variety of techniques, have attempted to estimate the mean daily intake of fluoride. Most have found intakes of 0.01 to 0.13 mg/kg body weight, with most mean intake values between 0.03 and 0.04 mg/kg body weight in non-fluoridated areas and 0.04 to 0.06 mg/kg body weight in fluoridated areas (NHS-CRD, 2000). However, individual intakes in children can greatly exceed the mean value, owing to ingestion of dentifrice, for example, Warren and Levy (1999), MRC (2002).

18. Fluorides are emitted to the atmosphere in both gaseous and particulate forms, but studies typically only report total fluoride content. In heavily polluted areas, typical daily inhalation intakes are in the range 10-40 µg/day (0.5-2 µg/m^3) and in some cases are as high as 60 µg/day (3 µg/m^3) (WHO, 2000). The major sources of hydrogen fluoride to air in the UK are coal fired power stations, coke production, brick production and primary aluminium production.

19. Fluoride remains in the surface soil indefinitely and contaminated soils pose a particular hazard to children, because of both hand-to-mouth behaviour and intentional ingestion of soil (pica), as well as indoor dust contamination (ATSDR, 2001).

2.3.2 Hydrogen fluoride inhalation

20. A study in rats suggests that removal of hydrogen fluoride from the inhaled air approaches 100% for exposures in the range 30 to 176 mg/m^3 (Morris and Smith, 1983). Mean urinary fluoride levels are linearly related to the hydrogen fluoride concentration in the air in occupational settings (Lund *et al.*, 1997). No data are available regarding the distribution of fluoride in the body following exposure to hydrogen fluoride only (ATSDR, 2001). The major route of fluoride excretion is via the kidneys and urine.

21. Populations living near industrial sources of hydrogen fluoride, including coal-burning facilities, may be exposed to higher levels of fluoride in the air. Vegetables and fruits grown near these sources may contain higher

levels of fluoride, particularly from fluoride-containing dust settling on the plants. In a coal burning area in China, endemic dental fluorosis was attributed to air pollution causing environmental contamination, including contamination of broad-leaf vegetables and stored water (Yixin *et al.*, 1993). The indoor burning of fluoride rich coal (with exposure to mainly hydrogen fluoride) also contributes to the overall fluoride intake. The reports are inadequate for establishing dose-response relations (ATSDR, 2001).

22. Skeletal fluorosis was first diagnosed in the Danish cryolite industry in 1932, where workers were exposed to elevated levels of hydrogen fluoride in the working atmosphere (Roholm, 1937). The available data on chronic toxicity from hydrogen fluoride exposure are mainly limited to studies of workers exposed to levels exceeding 2-2.5 mg/m^3, or a daily exposure to a worker of 20-25 mg. The Health and Safety Executive has set a time-weighted average work exposure limit of 1.5 mg/m^3.

2.4 Justification for a provisional guideline value for the systemic effects of hydrogen fluoride exposure

23. In the absence of a discernible threshold for the development of dental fluorosis, we used the results of a meta-analysis performed in a systematic review of water fluoridation by the NHS Centre for Review and Dissemination (McDonagh *et al.*, 2000) to estimate an appropriate lowest observed adverse effect level (LOAEL).

- They reported that 12.5% (95% confidence interval: 7.0-21.5%) of exposed people would have fluorosis of aesthetic concern at a fluoride level in drinking water of 1 ppm, with an overall prevalence of dental fluorosis of 18%.
- This finding was made in comparison with a theoretical low fluoride concentration of 0.4 ppm, even though many areas in Britain may have fluoride levels lower than 0.4 ppm.
- The difference between a water supply with low fluoride (0.4 ppm) and one containing 1 ppm is 0.6 ppm, which in a child drinking 1 litre of water a day represents an additional intake of 0.6 mg of fluoride per day, with all other sources of daily fluoride intake remaining constant.
- The Panel considers that an exposure in children aged one to six years to hydrogen fluoride at a concentration of 0.16 mg/m^3 in the ambient air (the guideline value it recommends against irritant effects on the respiratory system) would correspond approximately to an equivalent order of intake and so represents a LOAEL in children at an age when the dentine of the teeth is being formed. This assumes that the children breathe an estimated 4 to 6 m^3 of air per day. The Panel applied a further safety factor of ten as suitable for deriving a no observed adverse effect level (NOAEL).

- The Panel concluded that, at an air concentration below 0.016 mg/m^3, there would be a non-significant risk in a child of developing dental fluorosis of aesthetic concern as a result of living near a point source of hydrogen fluoride. This level corresponds to a daily intake in an adult of about 0.3 mg/day, which would be a negligible addition as far as the systemic effects on skeletal bone are concerned.
- A consultation by WHO on trace elements in human nutrition and health recommended that fluoride intakes in children aged one, two and three years of age should, if possible, be limited to 0.5, 1.0 and 1.5 mg/day, respectively (WHO, 1996). The daily intake by inhalation at the EPAQS recommended value would represent approximately 10% of these recommended total daily intakes.

2.5 Recommendation

24. The Panel recommends that concentrations of hydrogen fluoride not exceeding 0.02 ppm (0.016 mg/m^3) as a monthly average should protect against the systemic effects of fluoride on tooth enamel formation of aesthetic concern, as well as safeguard against any possible risk for skeletal effects.

25. It is unlikely that the ambient monthly mean would approach this value if the 1-hour guideline value for irritancy for hydrogen fluoride is not exceeded as an air pollutant emitted from a chimney stack. [1]

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[1] The conclusion is based on analysis of data for sulphur dioxide, which is also predominantly emitted from elevated point sources. An examination of measured sulphur dioxide concentrations at national network sites across the UK in 2004 shows that the maximum monthly mean concentrations for the year were on average 16 times lower than the hourly maximum for the year and more than ten times lower at 72% of sites.

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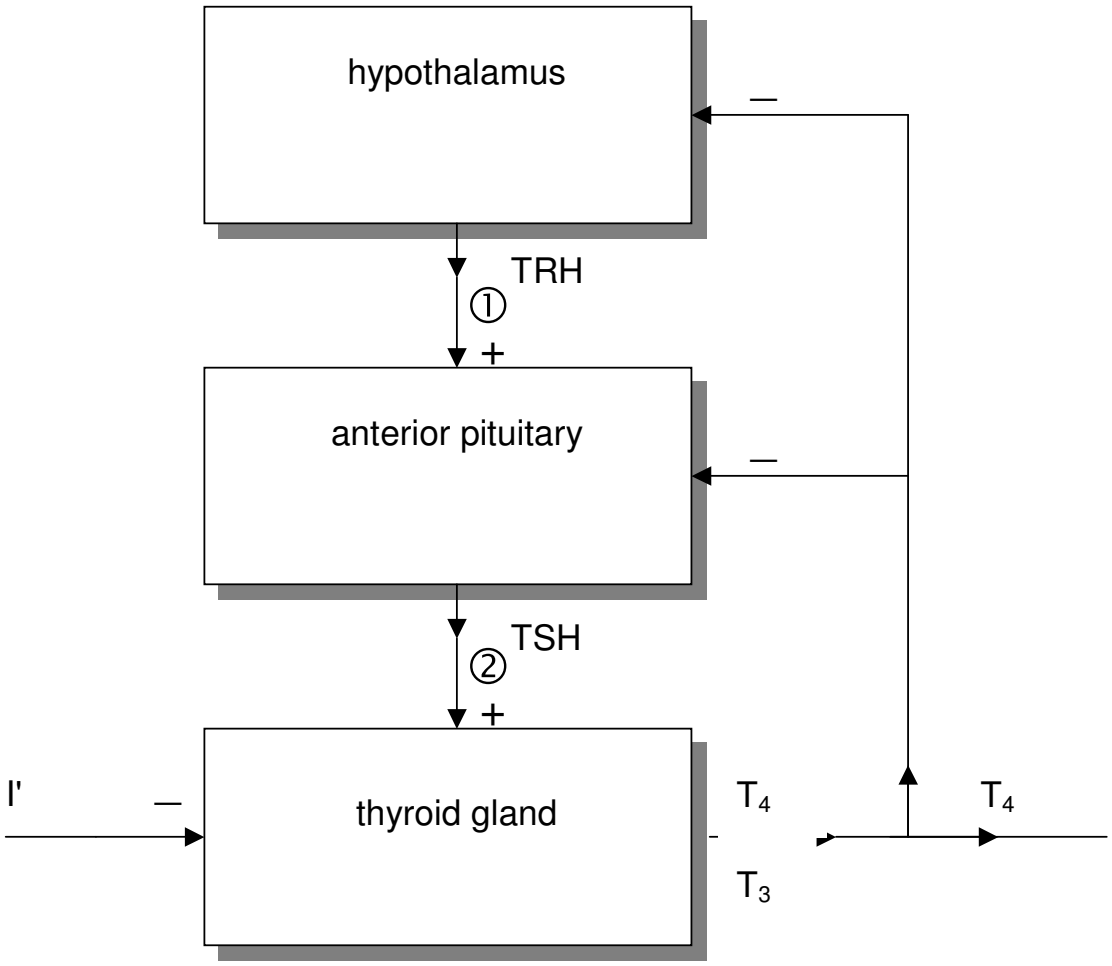
3 Long term exposure to hydrogen iodide

3.1 Thyroid metabolism

26. Iodine is an essential element required for the synthesis of the thyroid hormones, thyroxine (T4) and triiodothyronine (T3). A feedback mechanism exists linking the formation of thyroxine and triiodothyronine and the production of Thyrotropin Releasing Hormone (TRH) by the hypothalamus and Thyroid Stimulating Hormone (TSH) by the anterior pituitary gland respectively (see Figure). Triiodothyronine and thyroxine are produced in the thyroid from a precursor protein Thyroglobulin, also produced by the thyroid.



① T4 and T3 reducing the effect of TRH on the anterior pituitary

② T4 and T3 reducing the effect of TSH on the thyroid gland.

3.2 Sources of exposure to iodine

27. The main source of general population exposure to iodine is food and the information linking iodine to effects is derived from studies of dietary intakes. The results of studies with radioactive iodine suggest that systemic absorption of iodide from inhaled hydrogen iodide is likely to be as efficient as from iodine containing food (Zanzonico, 2000; Dawson *et al.*, 1985).

3.3 Iodine deficiency

28. Iodine deficiency can lead to enlargement of the thyroid (goitre) or, in severe cases in young children, to cretinism. Moderate iodine deficiency in pregnancy may adversely affect intellectual development in the baby. The daily intake of iodine recommended by the World Health Organisation (WHO) is 150 µg for adults (90 µg for pre-school children, 120 µg for children between six and 12 years in age, 250 µg for pregnant and nursing women). The typical UK intake is generally slightly lower than that recommended by the WHO. The European Commission's Scientific Committee on Food has advised that the tolerable upper intake level for iodine for adults (including pregnant women) is 600 µg/day.

3.4 Excess iodine intake

29. An excess of iodine in the diet can result in various disorders of thyroid function. At low levels of excess, the most common effect is hypothyroidism (under activity of the thyroid gland). This is described as the Wolff-Chaikoff effect and is due to

    - iodide inhibiting organic binding of iodide and thus reducing hormone synthesis
    - iodide inhibits the response of the thyroid gland to Thyroid Stimulating Hormone by reducing Cyclic Adenosine Monophosphate (cAMP)[2] formation
    - iodide reducing the breakdown of thyroglobulin to produce triiodothyronine and thyroxine.

30. These effects are most clearly seen when iodide transport is increased and explain the response of patients with hyperthyroidism (over activity of the thryroid gland) to iodine. Whether iodine excess leads to hypothyroidism or hyperthyroidism occurs depends on pre-existing iodine status.

3.5 Hypothryoidism

31. Overt hypothyroidism is associated with reduced thyroxine levels but subclinical or mild hypothyroidism may also arise in which thyroxine

[2] Cyclic Adenosine Monophosphate is an intracellular messenger molecule that allows cells to respond to hormones that are unable to pass through the cell membrane to enter a cell.

levels remain normal, but levels of Thyroid Stimulating Hormone are increased. Subclinical hypothyroidism may be associated with symptoms such as mood changes and lipid abnormalities that are not specific to hypothryoidism (Kek *et al*., 2000 and references therein). Some experts suggest a possible effect on cardiovascular health, but this is controversial (Kek *et al*., 2000 and references therein). Individuals with subclinical hypothyroidism are also at risk of developing overt hypothyroidism, and the risk is relative to the degree of elevation of Thyroid Stimulating Hormone concentration (Diez and Inglesias, 2004; Vanderpump *et al*., 1995; Rosenthal, 1987). There may be a continuum between those with purely biochemical subclinical hypothyroidism, those with mild symptoms of hypothyroidism but normal thyroxine levels and those with overt hypothyroidism.

32. Elderly women are most likely to develop hypothyroidism following a mild excess of iodine. The developing foetus and newborn baby are particularly susceptible to excess iodine intake (Laurberg *et al*., 2001) and were identified by the Expert Group of Vitamins and Minerals as a particularly sensitive group. Maternal subclinical hypothyroidism is thought to be associated with increased risk of foetal wastage and also impaired neurophysicological development of the newborn (Surks *et al*., 2004). Surks *et al*. do not demonstrate a link with excessive maternal iodine intake, but in a Japanese study, Nishiyama *et al.* (2004) demonstrated a link between high levels of maternal iodine intake and hypothyroidism in the new born. In a Chinese study, Li *et al.* (1997) demonstrated an association between long term exposure to a mild excess of iodine and subclinical and, more rarely, overt hypothyroidism, in school children. In another Chinese study, Gao *et al.* (2004) found an association between subclinical hypothyroidism in school children and excess iodine intake (210 ug/L in drinking water). Excessive iodine intake was also associated with adverse effects on IQ.

33. The results of studies undertaken in Newcastle and in Tayside suggest that between 0.2 and 0.3% of the UK population develop overt hypothyroidism each year compared with 0.01-0.08% who develop hyperthyroidism. The prevalence of hypothyroidism in Tayside is about 3% and of hyperthyroidism about 0.5% (Flynn *et al*., 2000). The prevalence of hypothyroidism is greater in women and in older age groups. About 1% of women over 60 in the UK develop overt hypothyroidism each year. The proportion of individuals with subclinical hypothyroidism is about two to three times greater than that showing overt hypothyroidism. Tunbridge *et al.* (1977) reported that the prevalence of subclinical hypothyroidism in women and men over 18 years of age in the UK is 7.5 and 2.8% respectively. Parle *et al*. (1991) reported in women and men over 65, the prevalence is 11.6 and 2.9% respectively. The prevalence members of the USA population older than 55 or 60 years is similar (Bagchi, 1990; Sawin, 1985). A proportion of these individuals may eventually develop hypothyroidism. A UK study showed that over half of patients with subclinical hypothyroidism developed overt hypothyroidism in a 20 year follow-up period with considerably higher risks for those aged 65 or more (Vanderpump *et al*.,

1995; Rosenthal, 1987). The results of studies undertaken elsewhere suggest that about 10% of patients with subclincial hypothyroidism are likely to develop overt hypothyroidism within a three to five year period (Diez and Inglesias, 2004; Engler *et al*., 1991).

34. Different populations appear to have different iodine tolerances depending on their typical long-term dietary intake of iodine. For example, some Japanese populations tolerate very high iodine intakes in fish and particularly as a result of consuming iodine rich seaweeds. The level of excess iodine intake associated with adverse effects is uncertain. There is some evidence that the prevalence of hypothyroidism is greater in countries or regions with high average dietary intakes of iodine than in areas with lower average intakes (Laurberg *et al*., 1998; Szaboics *et al*., 1997). Very low iodine intake also leads to hypothyroidism.

3.6 Studies of iodine supplementation

35. In studies of the effects of administering dietary supplements of iodine to volunteers, two 14 day studies undertaken in the USA showed no effects on thyroid function at 0.5 mg/day. Small but significant effects were found at 1.5 mg/day (Paul *et al*., 1988; Gardner *et al*., 1989). A third, 28 day study in women undertaken in the UK, however, showed effects at 0.5 mg/day (Chow *et al*., 1991). All three studies showed that iodine supplements could affect the thyroid function of normal volunteers and that effects arising from excess iodine intake are not confined to rare susceptible subgroups of the general population. There is no information about the longer term effects of iodine supplementation, so it is unclear whether the effects on thyroid function seen over 28 days would be maintained. It is also not clear whether the effects observed over 14 days or 28 days were reversible.

36. The Expert Group on Vitamins and Minerals have suggested that 0.5 mg of excess iodine per day would not be expected to have any significant adverse effects in adults, but did not adopt a formal guideline value for iodine. The Group believed that the changes in thyroid hormone activity seen in volunteers exposed to a dietary supplement of 0.5 mg/day represented a normal feedback process rather than an adverse effect. No uncertainty factors were applied in arriving at this figure because the data came from a number of well controlled studies in humans.

3.7 Recommendation

37. It seems plausible that a relatively small increase in iodine intake over a period of weeks to months could affect thyroid function in a small but significant (more than 1%) proportion of the population. The effects might be to both increase the prevalence of subclinical hypothyroidism and also to accelerate the progression from subclinical to overt hypothyroidism.

38. The lowest level of dietary iodine supplementation that has been observed to affect thyroid function in healthy adult volunteers in a 28 day

experiment is 0.5 mg/day. The clinical significance of the observed changes is unclear.

39. Current levels of iodine in air are believed to be extremely small. The Panel considered that it would be advisable to restrict the intake of iodine from ambient air to less than 0.5 mg/day as a monthly average. If allowance is made for the potentially greater susceptibility of people with subclinical hypothyroidism and/or the newborn/unborn child than the healthy volunteers used in experiments, a limit equivalent to an intake of 0.1 mg/day might be appropriate. Although it would be more usual to apply a factor of ten rather than five to allow for potentially susceptible populations, in this case, the Panel took account of the following circumstances:

    - The observed effect on thyroid function at 0.5 mg/day is very small;
    - The clinical significance of the effect is unclear and it may reflect an adaptation rather than an adverse effect.

40. For an average adult inhaling 20 m^3 of air per day, a daily intake of 0.1 mg would be equivalent to a hydrogen iodide concentration of 0.005 mg/m^3 = 5 $\mu g/m^3$ which is about 1 ppb.

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Abbreviations

cAMP	Cyclic Adenosine Monophosphate
EPAQS	Expert Panel on Air Quality Standards
L	litre
LOAEL	lowest observed adverse effect level
m^3	cubic metre (equivalent to 1000 litres)
µg	microgram (one millionth of a gram)
$\mu g/m^3$	micrograms per cubic metre
mg	milligram (one thousandth of a gram)
mg/m^3	milligrams per cubic metre
NOAEL	no observed adverse effect level
ppb	Parts per billion
ppm	Parts per million
SEPA	Scottish Environment 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 of continuous exposure or multiple doses over 24 hours or less.
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%).
Cyclic Adenosine Monophosphate (cAMP)	Cyclic Adenosine Monophosphate is an intracellular messenger molecule that allows cells to respond to hormones that are unable to pass through the cell membrane to enter a cell.
Dental fluorosis	A condition that results from excessive fluoride exposure that often causes the teeth to become discoloured and the enamel of the teeth to look spotted, pitted or stained.
Hyperthyroidism	A condition in which the thyroid gland produces more hormone than normal, resulting in an increased rate of metabolism, often with wasting of muscle and loss of weight together with restlessness and emotional instability.
Hypothalamus	In mammals the hypothalamus acts as the chief co-ordinating region of the autonomic nervous system and helps to regulate hormonal activity.
Hypothyroidism	A condition in which the level of thyroxine in the blood is abnormally low resulting in a decreased metabolic rate and which when severe causes cretinism (if the condition was congenital) and myxoedema (if acquired).
No observed adverse effect level (NOAEL)	A highest exposure level at which there are no statistically or biologically significant increase 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.
Skeletal fluorosis	An excessive accumulation of fluoride in bone associated with increased bone density and outgrowths.
Thyroglobulin	Produced by the thyroid gland.
Thyroid	A vascular body adjacent to the larynx and upper part of the trachea in vertebrates.
Thyroxine	A hormone secreted by the thyroid gland which increases the metabolic rate and regulates growth and development in animals.
Triiodothyronine	A thyroid hormone.