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Public Health Impacts of Exposure to Carbon Monoxide From Gas Appliances in UK Homes – Are We Missing Something?

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Key Words

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Abstract

Carbon monoxide (CO) is a colourless and odourless poisonous gas formed from the incomplete combustion of substances containing carbon. In the United Kingdom, over 22 million homes have mains or liquefied petroleum gas and consequently there is particular concern regarding potential CO poisoning resulting from malfunctioning domestic gas appliances. Although the number of reported cases of CO poisoning in the United Kingdom is relatively small, there is a high probability of misdiagnosis of the condition due to the ambiguous clinical symptoms of CO poisoning; incidence may therefore be much higher than currently reported. This review discusses the current knowledge on human health and toxicological effects following exposure to CO, focusing particularly on the public health impacts associated with gas appliances in UK homes. In determining the possibility of an underlying threat, the biological plausibility of misdiagnosis, in combination with reported cases, is discussed. The implication of misdiagnosis for public health treatment is also briefly summarised.

Introduction

Carbon monoxide (CO) is a colourless and odourless poisonous gas, formed from the incomplete combustion of organic compounds and fuels. The widespread use of fuel combustion for energy generation (e.g. cooking and heating appliances and vehicular emissions) and through cigarette smoking, make CO exposure a prevailing threat to human health. The common symptoms of CO poisoning include headache, nausea, vomiting, fatigue and generalised weakness and death. Furthermore, chronic low level exposure has been associated with symptoms

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similar to that of influenza or food poisoning, with high level exposure potentially leading to collapse and death [1]. Individual susceptibility to the plethora of health effects associated with CO exposure varies greatly among the population and has been extensively reviewed elsewhere [2–6].

This study was commissioned by the Gas Safe Register, with the objective of reviewing the current knowledge of CO toxicity, with an emphasis on public health impacts associated with gas appliances in UK homes. The study builds upon and extends the comprehensive literature base on CO currently available. The World Health Organisation (WHO) has reviewed the health effects and symptomatology, diagnosis, prognosis and misdiagnosis of CO poisoning associated with gas appliances [4,5], which provides a solid foundation on which to base this review; indeed few historical references are included here, unless specifically required to illustrate a particular issue.

The potential risk to health from CO in the home environment has been previously highlighted in the literature [7,8], and in the recent years, there has been an increased emphasis on the environmental assessment of buildings, particularly those associated with Green Building Certification Schemes such as Leadership in Energy & Environmental Design (LEED) and Hong Kong Environmental Assessment Method (HK BEAM), with indoor levels of CO being an integral part of those assessments [9]. The National Grid delivers gas to over 20 million homes in the United Kingdom [10] and, considering such widespread exposure, it is not surprising that there is potential for concern regarding CO poisoning, as a result of malfunctioning gas appliances. Currently, the number of reported cases of CO poisoning in the United Kingdom is relatively small, with approximately 50 cases of accidental death and 200 cases of non-fatal injury per year [11]. However, this statistic may be reduced through possible misdiagnosis, and it has been suggested that actual figures could be substantially higher [2]. This reporting fallacy was recently emphasised in letters from the UK Interim Chief Medical Officer, to Department of Health Colleagues on the 11 November 2010, which stated ''The number of people exposed to CO, but who are unaware of the cause and do not present at their GP's surgery or local hospital is still not known, but likely to be many more'' than currently reported [1].

Malfunctioning gas appliances have recently been implicated in the prevalence of CO poisoning cases in France, with data from the French CO poisoning surveillance system reporting 1,353 episodes of CO poisoning in 2007. Boilers (42.2%), water heaters (10.7%) and heaters (8.1%) were identified as the main domestic sources of CO emissions in France [12]. Similarly, Salameh et al. reported over half of CO poisoning in Jerusalem (1994–2006) to be attributable to faulty gas heaters in 292 hospital patients [13]. The association between fuel, heating and CO poisoning has been further established by emergency medical service data in Beijing, which identified elevated incidence of CO poisoning in winter months; 3,331 patients were recorded for CO poisoning between 2005 and 2007 in winter months, accounting for 88.4% of the study population [14].

Epidemiological methods can also be successfully utilised to assess risks to health from indoor air pollutants such as CO [15]. Such an investigation into early-life exposure to indoor air pollution and neuropsychological development in 482 preschoolers in Menorca, Spain during the period 1997–1999 has provided evidence that the use of gas appliances may have important public health implications. The study identified early-life exposure to indoor air pollution from gas appliances as a risk factor for impaired cognitive functioning and development of attention deficit hyperactivity disorder (ADHD). However, the role of CO was not discussed in isolation as the main focus of the study was nitrogen dioxide (NO_2) [16]. In a further study, the levels of CO in 384 coffee shops in Ankara were measured to assess risk to health of workers and clientele. Although the mean CO level overall was below both short- and long-term threshold values, in 34% of coffee shops monitored, CO levels were found to be above long-term threshold levels [17].

It is important to emphasise that the focal point of this review is the indoor domestic environment and underlying health impacts on the general population following exposure to CO through gas appliances. Although studies on outdoor air pollution have been included here, these are as a reference point for chemical transfer and diffusion throughout the environment where CO has been specifically measured and relevant health effects identified. Workplace, vehicle emission and cigarette smoking exposure are not considered within the scope of the study.

Health Effects and Symptomatology

Biological Mechanism of Toxicity

Carbon monoxide enters the blood via gaseous exchange in lungs. The binding affinity of CO is 240 times that of oxygen, meaning that CO readily combines with haemoglobin (Hb) to form carboxyhemoglobin

(COHb), significantly hindering the capacity to carry oxygen and reducing oxygen delivered to tissues. The transport and binding of CO to myoglobin and mitochondrial cytochrome enzymes, and in particular cytochrome A3, is thought to mediate CO toxicity. Furthermore, recent studies have suggested that CO may act as a local transmitter substance, controlling permeability of the micro-vasculature; increasing adhesion of inflammatory cells and platelets to the capillary endothelium [1].

Symptoms and Health Effects

Carbon monoxide is an endogenous breakdown product of haem, contributing approximately 0.5% of COHb concentration in the blood. In healthy, non-smoking individuals, basal COHb concentrations are typically less than 3% [6]. Toxicokinetic studies suggest that at COHb levels over 4%, each 1% incremental increase is associated with an approximate 1% decrease in oxygen consumption. Initial symptoms of CO exposure include decreased work capacity and compromised neurobehavioural functions and have been associated with serum levels of approximately 5% COHb; however, the first signs of overt CO poisoning are generally apparent when COHb concentrations exceed 10% [2].

With continued exposure to CO, clinical symptoms such as headache, shortness of breath and dilation of cutaneous blood vessels develop which, in an individual with coronary artery disease, may lead to acute coronary syndrome. More severe symptoms of CO exposure, typically reflected in serum COHb concentrations of 30–50%, include irritability, disturbed judgement, dizziness, poor vision, confusion and collapse or fainting on exertion; continued exposure can lead to unconsciousness, respiratory failure and death, with COHb concentrations above 80% being measured in fatal cases. It is important to emphasise however that there is significant interindividual variation in effect thresholds for CO exposure [2] and that humans may become acclimatised to low levels of CO following chronic exposure [18].

Several complications may arise following CO poisoning that give rise to delayed and/or protracted effects. Cardiovascular effects include hypotension, arrhythmias including sinus tachycardia, atrial flutter and fibrillation, premature ventricular contractions and ventricular tachycardia and fibrillation. Penney reported the prevalence of increased heart rate, stroke volume and systolic blood pressure, immediately following exposure [19]. Chronic CO exposure producing COHb levels of 10% or above can also lead to haemodynamic effects including polycythemia (increased erythrocyte number), increased blood volume and cardiomegaly (increased heart size). A study of Swedish men aged 34–49 years, who were either smokers, ex-smokers or had never smoked, investigated whether COHb level may be used as a marker for cardiovascular risk; follow-up of subjects was conducted over a 19-year period. In individuals that had never smoked, the COHb levels ranged between 0.13 and 5.47%. A level of above 0.67% was considered to be in the top quartile and was associated with a significantly higher incidence of cardiac events and deaths. The authors suggested that measurement of COHb levels could form part of the diagnosis assessment of cardiac disease [20].

In a recent U.S. multisite time-series study, Bell et al. estimated the risk of hospitalisation due to cardiovascular disease (CVD) from short-term CO exposure in over 9.3 million Medicare enrolees ($\geq$65) between 1999 and 2005 [21]. A positive and statistically significant association between same-day CO and elevated risk of CVD hospitalisation was observed. A 1-ppm increase in CO concentration, which approximates the interquartile range across communities, correlated to a 0.1–0.2% increase in mean blood COHb. The authors had provided the evidence that short-term exposure to ambient CO could pose a threat for public health, even below current US health-based regulatory standards [21]. Complications manifesting as neurological disturbances following acute CO exposure can include disorientation, confusion, coma, extremity flaccidity or spasticity. Delayed neuropsychiatric impairment may also become manifest over 3 weeks following CO intoxication [5]. Individuals exposed to high concentrations of CO have been seen to experience delayed neurological damage due to leukoencephalopathy, a condition caused by progressive toxic damage to the white matter of the brain [1].

Exposure Standards and Guidelines in the United Kingdom

The WHO recommends, for a wide range of air pollutants, guideline levels that should not be exceeded to protect the population against health effects [4]. For carbon monoxide, the guidelines are based on preventing a COHb level exceeding 2.5% (Table 1). This is to protect susceptible individuals and groups with documented or latent coronary artery disease, from CO concentrations that may induce acute coronary syndromes, heart rhythm disturbances or heart failure. Furthermore, as foetal Hb is known to have a higher binding affinity for CO and a more susceptible nervous system, the WHO guidelines also

Table 1. WHO Guidelines for CO levels in indoor air[a]

Concentration	Averaging time
90 ppm/100 mg·m^{-3}	15 min
50 ppm/60 mg·m^{-3}	30 min
25 ppm/30 mg·m^{-3}	1 h
10 ppm/10 mg·m^{-3}	8 h

CO: carbon monoxide, WHO: World Health Organisation.
[a]Adapted from Air Quality Guidelines for Europe, WHO, 2000 [4].

aim to protect foetuses of pregnant women from untoward hypoxic effects.

In the United Kingdom, the Air Quality Strategy sets out standards and objectives to control and improve ambient air quality [22]. This incorporates European Directive limit values as well as national air quality objectives. For CO the limit value is 10 mg·m^{-3}, which is equivalent to the UK objective expressed as a maximum daily running 8 h mean concentration. It is important to note that the conversion factor, 1 mg/m^3 = 0.873 ppm [22] has been applied throughout this study where the references cited reported concentrations of CO in air as ppm, to enable comparison and consistency.

In 2004, the Department of Health's Committee on the Medical Effects of Air Pollutants (COMEAP) reviewed available guidelines [3] and standards for CO and recommended that the same concentrations and averaging times recommended by the WHO (where indoor or outdoor air is not specified) [23] should be used as guidelines for indoor air quality in the United Kingdom. The average person spends 90% of their time indoors [24], which emphasises the need for public ambient air quality standards to be harmonised with outdoor air regulation. Importantly, newly built energy saving, air tight homes decrease the rate of ventilation with external environments, potentially bioconcentrating levels of CO (among other chemicals) by preventing diffusion and circulation of pollutants.

According to COMEAP, exposure to these guideline levels should not be harmful to the general public, but the safety of "sensitive" individuals cannot be guaranteed [3]. Exposure to levels above the guideline values would not necessarily mean that effects would be experienced; the guidelines contain a margin of safety and thus only very few people would be expected to experience adverse effects if levels of pollutants rise a little above the guideline or standard. With regard to occupational environments, the UK workplace exposure limits for CO are 35 mg·m^{-3} for long-term exposure (8-h time-weighted average) and 232 mg·m^{-3} for short-term exposure (15-min reference period) [25].

Public Health

Diagnosis and Treatment of CO Poisoning

This section focuses on the role of COHb in diagnosis. The requirement of a blood sample for determination of COHb levels presents a potential time constraint on speed of diagnosis and therefore time to treatment, which may impact on the overall success of recovery. The uses of novel technology to assess COHb levels non-invasively are illustrated in the case studies below. Such technology is useful in light of general difficulties in the diagnosis of CO poisoning (see "missed cases" section) and the absence of other, specific, physiological markers of exposure. Treatment of CO poisoning is currently by administration of 100% oxygen, which utilises the reversible nature of CO binding to Hb. Under normal conditions, COHb has a half-life in blood of 320 min, potentially leading to damage of neuronal networks and depleting available oxygen for tissues. Following administration of 100% oxygen, half-life is reduced to 80 min, while 100% oxygen at two atmospheric pressures (hyperbaric oxygen) can reduce the half-life of COHb to 23 min [1]. In addition, hyperbaric oxygen treatment can facilitate removal of CO from myoglobin, cytochrome oxidase and other proteins within the cellular compartment. The use of hyperbaric oxygen therapy is also discussed in comparison with normobaric oxygen in the following section.

Diagnostic and Prognostic Tools

The literature describes a plethora of diagnostic and prognostic tools for the determination of CO toxicity. A new non-invasive approach to the measurement of CO exposure has recently been reported. The Rad-57 pulse CO-oximeter (by Masimo Inc.) is a non-invasive finger probe that measures COHb levels. This device has been used in an unpublished study by the London Ambulance Service in the United Kingdom [26] and also in a published study from an emergency department in the United States, in which diagnoses were made both in patients presenting with non-specific symptoms and in accompanying partners who were asymptomatic. This latter report suggests that due to the rapid and non-invasive nature of the COHb measurement, use of this device has the potential to detect cases of CO poisoning that could be missed when relying on blood COHb sampling alone [27]. However, it should be noted that both false positive and negative cases have

been reported using such devices and therefore, at present, all results require confirmation through blood tests.

A study in the United States analysed the number of hospitals with the facility to measure blood COHb on site [28], and conversely where blood samples needed to be sent to a separate laboratory. Results from the assessment of COHb were obtained in 10 ± 10 min in hospitals with onsite facilities and in 904 ± 1360 min (i.e. ~15 h) in hospitals without onsite facilities; delays in COHb assessment may result in low estimates of exposure. Over 90% of patients referred for hyperbaric treatment were from hospitals with onsite COHb measurement facilities. The authors suggested that the capability to measure COHb levels on site could impact on the number of patients being diagnosed and/or treated for CO poisoning. In the United Kingdom, hyperbaric oxygen treatment is recommended at serum COHb concentrations exceeding 20%. However, level of COHb measured will depend on time delay in monitoring as chemical equilibrium will establish post exposure, decreasing COHb in the blood [1]. This study supports the conclusion of Chee et al. that rapid measurement of COHb could aid the diagnosis and thus treatment of CO poisoning [27]. The efficacy of oxygen treatment and evidence for increased treatment affectivity following prompt treatment is generally accepted in the literature [28].

A plethora of COHb monitoring and assessment techniques have been reported. In a controlled study of 15 healthy subjects and 15 CO poisoning patients, electrocardiogram (ECG) and a range of biomarkers of endogenous cardiac markers, that may be secreted upon myocardial stress, were evaluated. Correlation between COHb and cardiac hormones was investigated. There was a positive correlation between COHb and N-terminal pro brain natriuretic peptide (NT-proBNP) and also between COHb and creatine kinase. The authors suggested that plasma NT-proBNP may be utilised as a diagnostic marker of cardiotoxicity following CO poisoning [29]. Kinoshita et al. reported the use of serial diffusion-weighted magnetic resonance imaging (MRI) for early identification of acute CO poisoning effects in a 35-year-old man who subsequently developed pallidoreticular damage and delayed leukoencephalopathy [30].

In Hong Kong during the period 1999–2002, 148 cases of CO poisoning as a result of charcoal burning were identified. Twenty-five individuals were unconscious upon arrival at hospital; of these, 12 had neurological complications and 5 had delayed neurological sequelae. Blood results showing hyperkalemia and acidosis were associated with unconsciousness upon arrival and greater duration of stay in hospital. Hyperkalemia, acidosis and unconsciousness were considered to be valuable prognostic factors of CO exposure [31].

In a recent study, Rissanen et al. demonstrated that diagnosis of presynaptic, dopaminergic hypofunction in putamen (which is a part of the globus pallidus region of the brain, associating with the corpus striatum and receiving signals from the suppressor centres of the cortex) could be confirmed using fluoro-I-dopa positron emission tomography (PET) imaging in a 29-year-old male patient with extrapyramidal syndrome caused by CO poisoning (or another sudden neurotoxic insult) [32]. Clinically, the parkinsonian symptoms resolved 1.5 years following poisoning, emphasising the long-term health repercussions of acute CO exposure, and the application of three dimensional imaging of functional processes in CO toxicity.

Treatment

Therapy for CO poisoning involves treatment with 100% normobaric oxygen – or hyperbaric oxygen if considered appropriate. However, there is currently a mixed opinion on the merits of normobaric compared with hyperbaric oxygen treatment. In a study of 26 patients with acute CO poisoning, the restorative effects of normobaric or hyperbaric oxygen were compared. As well as COHb levels, the effects of CO poisoning on the inhibition of mitochondrial complex IV was measured as a restorative endpoint. The patients were separated into severe (COHb = over 20%) or moderate (COHb = 10–20%) poisoning groups. Severely poisoned patients were randomly treated with one or two sessions of hyperbaric oxygen and moderately poisoned patients randomly treated with one normobaric or one hyperbaric oxygen session. Assessments were made up to 3 months after treatment. Mitochondrial complex IV activity was decreased in severe and moderate patients compared with controls; however, there was no difference between moderate poisoning patients that had received normobaric or hyperbaric oxygen. Similarly, there was no difference in severe patients that received one or two sessions of hyperbaric oxygen. However, recovery of mitochondrial complex IV with time was noted in all groups except for the moderately poisoned group that received only normobaric oxygen. Overall, in severely poisoned patients, a single session of hyperbaric oxygen restored mitochondrial complex IV activity and was more effective than normobaric oxygen in moderately poisoned patients [33]. Recently reviewed by the National Health Service (NHS), hyperbaric oxygen treatment was recommended

following diagnosis of CO poisoning and considered a cost-effective approach at £32–£41 per 90-min treatment at 2.2–3 atmospheric pressures [34].

However, although the use of hyperbaric oxygen is preventative of neurological damage, quickly removing CO from the blood, there are associated health risks. A study investigating hyperbaric oxygen related seizures has been reported. Seizures from hyperbaric therapy are generally rare, but in cases of CO poisoning, a certain number of risk factors for hyperbaric therapy associated seizures are known; these include fever, hypothermia, anxiety, prior seizure and traumatic brain injury. This report considers two cases of seizures from hyperbaric therapy where there were no known risk factors. Such seizures are usually self-limiting, and Sanders et al stated that physicians should not be dissuaded from ordering hyperbaric oxygen therapy for CO poisoning, despite this possible side effect [35].

Throughout the past decade, the predicament of normobaric versus hyperbaric oxygen treatment (HBO2) in CO poisoning treatment has been complicated by contradictory reports in the literature. Weaver et al. reported CO poisoning to cause cognitive sequelae, which was reduced by hyperbaric oxygen treatment [36]. However, Scheinkestel et al. compared the neurological sequelae in patients after treatment with hyperbaric or normobaric oxygen, reporting worse neurologic outcomes and further treatment in hyperbaric treatment groups [37]. Furthermore, in letters to the British Medical Journal, Weaver queried Scheinkestel et al.'s methodology stating that "I am unaware of anyone who treats acute poisoning with 100% oxygen for 2–3 days, apart from Scheinkestel et al. in their trial" identifying this variance in methodology may contribute to the observed differences [38].

Although the reporting of hyperbaric oxygen therapy is now fairly commonplace, there remains caution as to which cases should be given hyperbaric oxygen treatment and which should not, in the best management of CO poisoning [39]. Moreover, successful removal of CO by oxygen treatment does not guarantee full recovery, and neurological symptoms can develop weeks after intoxication and associated treatment. Furthermore, it has been suggested that the cause of neurological sequelae may be misdiagnosis in the first instance [40] and inadequate or delayed therapy [41]. It has been suggested that if oxygen is applied within 6 h of intoxication, complete recovery is more likely [42].

In summary, the traditional means of identifying CO exposure as the cause of poisoning is to measure COHb levels in blood samples. However, this would entail various disadvantages, and in particular the length of time that may elapse between exposure and a blood sample being taken, during which time COHb concentration could well have fallen back to near normal levels, preventing appropriate treatment. To overcome this, a non-invasive CO-oximeter (finger probe) has been developed for the instantaneous measurement of COHb concentrations. Other diagnostic markers have been proposed or are being developed, including MRI and NT-proBNP. Hyperkalaemia, acidosis and unconsciousness have been considered as valuable prognostic factors.

Missed Cases

Due to the broad-ranging non-specific symptoms of CO intoxication, the number of missed cases could be considerable, particularly where exposure is chronic and at low levels. Detecting CO exposure, raised COHb and/or clinical symptoms of CO poisoning are important factors that would aid identification of cases of CO poisoning. Possible misdiagnoses in patients with CO poisoning are summarised in Table 2.

In an unpublished summary of a London Ambulance Service report [26], 83 cases of unsuspected CO poisoning cases were reported. This may be considered as an underestimation of the total number of missed cases, however, because only five ambulance crews were equipped with pulse CO-oximeters for COHb measurement, and the total number of patients that were assessed for CO poisoning is unknown. Therefore, whilst this report provides clear evidence that many CO poisoning cases are undiagnosed in the United Kingdom, derivation of the potential total number of missed cases nationwide is not possible from these data.

Annual reports by the Health and Safety Executive (HSE) have documented accidental domestic CO poisoning incidents due to emissions released from piped natural or liquefied petroleum gas, using data gathered in a voluntary reporting scheme [43]. For example in 2003–2004, Transco (which was re-named National Grid Gas plc. in 2005) issued 183 incident notification forms, which gave details of CO poisoning events. A total of 87 diagnosed CO intoxicated patients and 36 incidents in Great Britain (GB) were identified. There were, in total, 8 fatalities and 79 non-fatal patients. Of these 79 patients, 13 required immediate hospitalisation for more than 24 h, 61 required immediate hospitalisation for less than 24 h and/or hospital tests and 5 required other medical treatment. The majority of all CO incidents (27 out of 36) involved appliances that were fitted with open, individual, natural draught flues. Central heating appliances (generally fired

Table 2. Some possible misdiagnoses in patients with CO poisoning

Symptom caused by CO exposure	Alternative diagnosis
Neurological	
Cerebral ischaemic accident due to CO poisoning	Cerebrovascular accident
Headache	Migraine, tension headache
Convulsions	Epilepsy
Vomiting, headache, bizarre neurological symptoms	Meningitis, encephalitis
Late-onset Parkinsonian symptoms	Parkinsonism
Psychiatric	
Lethargy, somatic symptoms	Depression
Hyperventilation, headache, malaise	Anxiety state
Confusion, hallucinations	Acute confusional state
Cardiac	
A critical coronary artery lesion exacerbated by CO toxicity	Myocardial infarction
Conduction system hypoxia	Cardiac arrhythmias
Arrythmia from CO toxicity	Primary arrhythmia
Pharmacological and toxicological	
Hypoxic coma, non-traumatic rhabdomyloysis	Drug overdose
Coma and renal failure	Ethylene glycol poisoning
Vomiting, ataxia, slurred speech, coma	Ethanol intoxication
Agitation, confusion, hallucinations	Drug abuse
Infections	
Muscle aches, tachypnoea, headache, exhaustion	Influenza and other viral Infections
Lethargy, myalgia	Post viral syndrome
Nausea and vomiting	Gastroenteritis and food
Dyspnoea, delirium	Poisoning
Headache, malaise	Pneumonia; Sinusitis
Others	
Abdominal pain, nausea, vomiting	Cholecystitis and other acute abdominal conditions

CO: carbon monoxide.
[a]Adapted from Lowe-Ponsford and Henry, 1989 cited in Green et al., 1998 [6].

by piped natural gas) featured in 31 of the 36 incidents, which equates to 86% [43].

By comparison, in 2005–2006, only 15 incidents were reported in total, with 7 fatalities and 16 non-fatal casualties – of which 3 required immediate hospitalisation for more than 24 h, 8 required immediate hospitalisation for less than 24 h and/or hospital tests, 2 required other medical treatment and 3 required no (or refused) medical treatment. Similar to the 2003–2004 report, the majority of incidents (9 from 15) involved open, individual natural draught flue appliances, and central heating appliance incidents accounted for 74% (17 of 23) fatal and non-fatal casualties [44]. The most common causes of incidents noted in the reports from both 2003–2004 and 2005–2006 reports were lack of servicing and flue/terminal faults. Flue and ventilation faults as well as appliance faults were also commonly considered the cause of many domestic incidents. As suggested by these two reports, whilst cases are certainly still being reported, the overall numbers of incidents during the years of monitoring (1996–2006) have declined from 70 in 1996–1997 to 15 in 2005–2006 [43,44], possibly indicative of improvements to fuel burning logistics. However, as the scheme was voluntary, the actual numbers are likely to be higher. Furthermore, the latest HSE report states that the reported figures are much lower than those published on the HSE website. According to the website figures, in 2005–2006 there were 16 fatalities and 210 non-fatal casualties (compared to 7 and 16, respectively, in the HSE report for 2005–2006). The reasons for this discrepancy were not fully explained, but one of the contributing factors is that the inclusion criteria for the voluntary reporting scheme were generally narrower; for example, incidents in commercial properties are not included in the voluntary reporting scheme [44].

The HSE recommend continued collection and analysis of data from CO poisoning cases. In the absence of such information, safe operation of gas appliances cannot be quantified or repeated occurrences properly identified. Furthermore, the long term-use of gas appliances and the impact of changes to installation standards cannot be accurately assessed. The HSE emphasises the need for concerned parties, such as those involved with installation and maintenance of gas supply, to be regularly informed about findings from the analysis of CO incidents.

The potential underestimation of the number of CO poisoning cases has been highlighted also in other countries. For example, a review by Sanchez et al. discusses CO poisoning in Spain and speculates that approximately one third of non-lethal CO exposures are not recognised [45]. A single case has been reported of a healthy 25-year-old female in Taiwan presenting with headache, nausea, vomiting and paroxysmal atrial fibrillation. COHb was not assessed, and as all other parameters were found to be normal, the patient was discharged. This same patient returned to hospital 4 h later due to unresponsiveness and at this point her blood COHb was measured as 43.2%. The authors discussed the difficulty of CO poisoning diagnosis due to diverse and easily confusable symptoms, emphasising the need for cheap standard monitoring techniques [46].

Overall, it is clear from the cases described above that the symptoms of CO poisoning are very easily confused with many other ailments. In addition, levels of COHb are not measured as a matter of course in all emergency department admissions and as there is no other definitive method to identify CO intoxication, many cases of CO poisoning may be missed.

''Occult CO poisoning'' is a term used to define cases of exposure and poisoning that may never come to the attention of the medical practitioner. In a study by Suner and colleagues in the United States [47], the frequency of confirmed occult CO poisoning in the studied population (which comprised 14,438 patients, of whom 10,856 (75%) received screening for COHb by a pulse CO-oximeter) was found to be approximately 4 per 10,000 patients (0.04%) in the winter months (December to March) and 1 per 10,000 patients (0.01%) in the summer months (April to July). Using data from the Centers for Disease Control and Prevention that showed there were 110 million emergency department visits in the United States in 2004, the authors calculated that there could be the potential for at least 11,000 occult poisoning cases to go undetected annually in the United States.

Extrapolation of these values to the 19,588,017 accident and emergency attendances in England during 2008–2009 [48], would indicate that the potential numbers of missed cases would be at least 1,959 per annum – equating to approximately 2,000 missed cases across the whole of the United Kingdom. However, the differences in use of fuel, use and maintenance of gas appliances, housing characteristics and legislation in the United States compared with the United Kingdom (and other factors influencing exposure) have not been accounted for in this estimation. The validity of extrapolation from the United States to the United Kingdom is therefore very uncertain and new studies are required to ascertain actual figures for the United Kingdom.

Potential Health Impacts of Indoor Gas Appliance Use in the United Kingdom

It is known that faulty domestic cooking and heating appliances inadequately vented to the outside can cause high indoor concentrations of CO, and health risks associated with CO poisoning are nearly always associated with the incorrect use of combustion devices, or faulty unvented gas appliances [2].

Basarab et al. reviewed current approaches to surveillance of CO incidents in the United Kingdom [49] and identified the three main current data sets:

- Office of National Statistics (ONS) data; mortality data arising from reports to the coroner of all suspected or confirmed deaths from CO poisoning.
- Hospital Episode statistics; data collected by the NHS information centre on admitted patients but it does not consistently distinguish accidental and non-accidental incidents. Accident and Emergency (A&E) data collection has also been initiated.
- Health and Safety Executive (HSE) data; incidents where someone has died or suffered a major injury attributed to CO in connection with gas (but not other fuels) that are reported to HSE under the reporting of injuries Diseases and Dangerous Occurrences legislation).

The authors discuss how the existing data sets, combined with other data sets and ongoing work to improve reporting during acute incidents and liaison across agencies, could provide a platform for an effective public health surveillance system.

Mandal et al. reported the development of a decision support toolkit for local Health Protection Units in the United Kingdom to assist the management of CO incidents [50]. They discussed the difficulties of defining a case by taking account of a combination of clinical features, environmental monitoring and biological levels. They examined data for CO incidents recorded on the Health Protection Agency Chemical Hazards and Poisons Division (CHaPD) incident log between 2006 and 2007 and noted that while most of the 47 potential or actual CO incidents were related to faulty domestic gas central heating appliances, for many the source was not documented. The authors also refer to casualties (218) and fatalities (50) from CO incidents reported by CORGI for the period January 2006 to April 2007 [51].

As part of a review of the benefits of providing CO detectors in homes, a detailed analysis has been conducted of deaths, injuries and reportable incidents concerning all fuels over recent years [51]. Annual deaths from CO poisoning totalled approximately 250 in 2007 although about 170 of these were considered to be associated with suicide. About half of the remaining 80 were attributable to CO from a combustion device. As the ONS database does not distinguish the type of home, other databases were also assessed; data on deaths published by the Carbon Monoxide and Gas Safety Society highlighted a disproportionately high incidence of cases in caravans and boats compared to dwellings [51]. The authors found that it was difficult to link incidents to fuel type with the available data. The HSE recorded death and injuries arising from gas and LPG fuelled appliances combined (10 deaths and 184 injuries in 2006–2007) [36]. The Solid Fuel Association recorded four deaths and eight injuries in 2006–2007 due to CO from solid fuel appliances (coal, biomass and barbeques) [44].

Based on extrapolation of data from home visits by gas emergency engineers related to CO in domestic dwellings in 2008, the authors estimated a CO occurrence in 0.2% of homes with gas (i.e. 40,000 homes). The report included a cost benefit analysis of installing CO detectors alongside new gas appliances and recommended that this be undertaken except where the gas and LPG appliance conforms to the European Gas Appliance Directive, or where a pressure jet oil appliance is installed [51].

The study by Croxford et al. of 270 homes in London included a visit to 50 of the properties with relatively high CO concentrations to check the performance of the gas appliances [52]. Nearly 5% of the total sample of homes was found to have at least one element of at least one gas appliance that could be considered dangerous by the visiting gas engineer. The authors concluded that there may be a significant number of homes with dangerous gas appliances. They speculated that with one million fuel poor and vulnerable homes in the United Kingdom and 83% of all UK homes using gas, a conservative estimate is that at least 39,000 homes have appliances that might pose a considerable risk of exposing occupants to elevated CO levels [52]. It should be noted, however, that this study had a low sample size and that the extrapolated figures could have a substantial margin of error.

A later study by the same authors, also based in London, United Kingdom, assessed the incidence and correlation of self-reported neurological symptoms and CO emissions due to poor quality gas appliance installations [53]. In 2006 (April–June), 597 homes had all gas appliances checked and the safety status assessed. Housing was mainly in old urban areas with a high percentage (72%) of terraced homes, most being built between 1918 and 1939. A total of 50% of homes in the sample had at least one resident over 65 years of age. Appliances were categorised as ''at risk'', ''immediately dangerous'', ''not to current standards'' or ''no exposure''. Levels of CO emitted from an appliance, together with its use and features were categorised as ''high'' or ''very high'' exposure – which indicated that occupants were likely to be exposed to $>30\,mg{\cdot}m^{-3}$ CO per hour – through to ''no exposure'' likelihoods. The self-reported symptoms at each level of exposure were compared with the symptoms reported at the lowest exposure level. Results showed a significant association between high or very high exposure and self-reported symptoms, compared with ''no exposure'' likelihoods. Overall this study identified an association between prevalence of self-reported neurological symptoms and risk of CO exposure at low concentrations. The authors suggested that ~1% of all homes with gas appliances might have householders suffering neurological symptoms that may be caused by exposure to CO from their gas appliances. As the association was based on self-reporting further investigation may be required [54]. Approximately 22 million homes in GB have mains gas or liquefied petroleum gas [51], which equates to a potential total of approximately 200,000 homes where CO exposure from gas appliances is possible. The homes sampled in both this study and the study previously described, by Croxford et al. [52], were all based within the London area. The representativeness of these homes for extrapolation to the United Kingdom as a whole is therefore debatable and highlights the limited availability of UK data, underlining the need for additional research.

Table 3 summarises the studies on risks to public health described in this section. Some published studies detailed in this table do not report the source of CO in the poisoning cases and thus further breakdown of figures to derive the numbers of cases/individuals where CO poisoning was specifically from gas appliances is not possible.

Conclusions

It is clear that the most effective form of protection from CO poisoning is the prevention of inappropriate exposure. Although CO intoxication can be treated effectively with normobaric (or hyberbaric) oxygen, in some cases treatment does not reverse all the symptoms

Table 3. Summary of CO information addressing risks of CO exposure to public health

Reported case	Extrapolation
Number of malfunctioning appliances	Estimated number of CO occurrences in homes based on Gas Emergency Service CO-related call-outs equates to 40,000 or 0.2% of homes in GB [51] Estimated that at least 39,000 homes could have a "problem" gas appliance [52]
Number of fatalities from CO poisonings in the United Kingdom	Annual deaths from CO in United Kingdom in 2007 were 250. Of these, 170 were due to suicide. Of the remaining 80, only half were due to combustion devices, which leaves 40 deaths [51] 50 fatal and 218 non-fatal confirmed CO poisoning cases in the United Kingdom in 2006 [50]
Estimation of missed cases	In an American study, confirmed occult CO poisoning cases of 0.01–0.04% of emergency department admissions were identified [47] In England in 2008–2009, there were 19,588,017 [48] emergency department admissions. Application of the U.S. rates would give an estimation of at least 1,959 "hidden" cases, that is the order of 2000 in the United Kingdom
Estimated number of homes with gas appliances with CO exposure symptoms	Approximately 1% of homes are estimated to have gas appliances that may have householders suffering symptoms of CO exposure from gas appliances [54]. With approximately 22 million homes in GB having mains gas or liquefied petroleum gas [51], this equates to approximately 200,000 homes where CO exposure from gas appliances is possible

CO: carbon monoxide; GB: Great Britain.
From CLG [51]; Croxford [52]; Suner et al. [47]; Croxford et al. [54].

and in severe cases long-term effects are apparent. The literature also highlights the possibility of an underlying epidemic of tiredness, reduced cognitive function and dizziness resultant of low-level chronic exposures to CO. Occult CO poisoning may greatly affect the happiness and mental well-being of individuals, but remain unnoticed throughout the population.

Furthermore, it is evident from the literature reviewed here, that misdiagnosis of CO poisoning may be a common quandary due to the non-specific symptoms of CO poisoning. Improved awareness by medical professionals is therefore essential. This is especially important when non-specific symptoms are presented and cohabitants have related symptoms, as this may be indicative of malfunctioning gas appliances in the home, that pose a continuing threat to health.

Studies have demonstrated that the use of non-invasive pulse CO-oximeters is effective in the diagnosis of unsuspected CO intoxications and may also be useful for early diagnosis and treatment of suspected cases. However, the delay in monitoring remains a significant limitation of detection. Blood COHb levels will decline rapidly following detachment from the CO source; the perceived levels may therefore not be representative of exposure, nor the binding of CO to mitochondrial cytochromes, which may greatly affect the long-term effects associated with CO exposure.

Published studies indicate that there may be a considerable number of homes with potentially faulty gas appliances in the United Kingdom, in combination with the fact that we spend an estimated 90% of our time indoors, there is scope for significant chronic low level exposure. However, the reliability of available data regarding the number of households that may be at risk is limited. Current studies reflect low sample sizes and limited geographical area, and therefore the representativeness of the data for application to the United Kingdom as a whole is questionable. In addition, only a few studies, which have not been conducted in the United Kingdom, have investigated potential numbers of missed cases of CO poisoning. Nonetheless, the literature supports the potential for missed CO poisoning cases, emphasising a need for additional research to inform a more exact and quantitative assessment of the risk of CO exposure and poisoning from gas appliances in the United Kingdom.

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References

1 UK Department of Health: Letters from the Interim Chief Medical Officer and the Chief Nursing officer: Carbon monoxide poisoning: Needless deaths, unnecessary injury. PL/CMO/2010/02, UK, 2010.
2 European Commission: The INDEX project: Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU. Final Report, European Commission, Joint Research Centre, Institute for Health and Consumer Protection, Physical and Chemical Exposure unit, I-21020 Ispra (VA), Italy, 2005.
3 UK Department of Health: Guidance on the effects on health of indoor air pollutants, Committee on the Medical Effects of Air Pollutants, 2004.
4 WHO: Carbon monoxide; in Air Quality Guidelines for Europe, 2nd ed, WHO, Geneva, 2000, pp. 75–79. Available at: http://www.euro.who.int/document/e71922.pdf.
5 WHO: Carbon monoxide. Environmental Health Criteria EHC 213, World Health Organisation, Geneva, 1999.
6 Green E, Short S, Shuker LK, Harrison PTC: Carbon monoxide exposure in the home environment and the evaluation of risks to health: Indoor Built Environ 1999;8:168–175.
7 Croxford B, Hutchinson E, Leonardi GS, McKenna L, Nicholson L, Volans G, Wilkinson P: Real time carbon monoxide measurements from 270 UK homes; in Raleigh JJ (eds): Proceedings of Indoor Environmental Quality (IEQ) – Problems, Research, and Solutions, Air and Waste Management Association (A&WMA) and US EPA's Office of Research and Development, North Carolina, USA, 2005.
8 Raw G, Coward S, Brown V, Crump D: Exposure to air pollutants in English homes: J Exposure Anal Environ Epidemiol 2004;14:S85–S94.
9 Yu CWF, Kim JT: Building environmental Assessment Schemes for Rating of IAQ in sustainable Buildings: Indoor Built Environ 2011;20(1):5–15.
10 The National Grid: Who are National Grid? Available at: http://www.nationalgrid.com/UK/gas/About/Who+are+National+Grid/ (accessed June 11).
11 Department of Health, UK: Letters from the Interim Chief Medical Officer and the Chief Nursing officer: Recognising Carbon Monoxide Poisoning – 'Think CO'. PL/CMO/2008/8, PL/CNO/2008/8, UK, 2008.
12 Verrier A, Delaunay C, Coquet S, Théaudin K, Cabot C, Girard D, Daoudi J, de Bels F: Carbon monoxide poisoning episodes in metropolitan france in 2007: Bulletin Epidemiologique Hebdomadaire 2010;1:1–5.
13 Salameh S, Amitai Y, Antopolsky M, Rott D, Stalnicowicz R: Carbon monoxide poisoning in Jerusalem: epidemiology and risk factors: Clin Toxicol (Phila) 2009;47(2):137–141.
14 Du T, Zhang Y, Wu JS, Wang H, Ji X, Xu T, Li Y, Xu L, Lewin MR: Domicile-related carbon monoxide poisoning in cold months and its relation with climatic factors: Am J Emergency Med 2010;28(8):928–932.
15 Brown T, Holmes P, Harrison PTC: The applicability of epidemiological methods to the assessment of the risks to human health of indoor air pollution: an overview: Indoor Built Environ 2010;19(3):311–326.
16 Morales E, Julvez J, Torrent M, de Cid R, Guxens M, Bustamante M, Kunzli N, Sunyer, J: Association of early-life exposure to household gas appliances and indoor nitrogen dioxide with cognition and attention behavior in preschoolers: Am J Epidemiol 2009;169(11):1327–1336.
17 Tekbas OF, Gulec M, Odabasi E, Vaizoglu SA, Guler C: Determination of carbon monoxide levels in coffee shops in Ankara: Indoor Built Environ 2009;18(2):130–137.
18 EM Killick: The acclimatization of the human subject to atmospheres containing low concentrations of carbon monoxide: J Physiol 1936;87(1):41–55.
19 Penney DG: Hemodynamic response to carbon monoxide: Environ Health Perspect 1998;77:121–130.
20 Hedblad B, Engström G, Janzon E, Berglund G, Janzon L: COHb% as a marker of cardiovascular risk in never smokers: results from a population-based cohort study: Scand J Public Health 2006;34(6):609–615.
21 Bell ML, Peng RD, Dominici F, Samet JM: Emergency hospital admissions for cardiovascular diseases and ambient levels of carbon monoxide results for 126 united states urban counties, 1999-2005: Circulation 2009;120(11):949–955.
22 DEFRA: The Air Quality Strategy for England, Scotland, Wales and Northern Ireland, Vol. 2, HMSO, Norwich, July 2007.
23 WHO: Carbon monoxide – Air Quality Guidelines for Europe; in WHO: Air Quality Guidelines for Europe, Copenhagen, Denmark, 1987, pp. 210–220.
24 Yu C, Crump D: Indoor environmental quality – standards for protection of occupational safety, health and environment: Indoor Built Environ 2010;19(5):499–502.
25 Health and Safety Executive: Workplace exposure limits EH40/2005, 2007. Available at http://www.hse.gov.uk/coshh/basics/exposure-limits.htm (accessed June 9, 2011).
26 London Ambulance Service, NHS Trust: A Feasibility Study into Pre-Hospital Carbon Monoxide Monitoring of Patients: Unpublished, 2009.
27 Chee KJ, Nilson D, Partridge R, Hughes A, Suner S, Sucov A, Jay G: Finding needles in a haystack: a case series of carbon monoxide poisoning detected using new technology in the emergency department: Clin Toxicol (Phila) 2008;46(5):461–469.
28 Hampson NB, Scott KL, Zmaeff JL: Carboxyhemoglobin measurement by hospitals: implications for the diagnosis of carbon monoxide poisoning: J Emergency Med 2006;31(1):13–16.
29 Davutoglu V, Gunay N, Kocoglu H, Gunay N, Yildirim C, Cavdar M, Tarakcioglu M: Serum levels of NT-ProBNP as an early cardiac marker of carbon monoxide poisoning: Inhalation Toxicol 2006;18(2):155–158.
30 Kinoshita T, Sugihara S, Matsusue E, Fujii S, Ametani M, Ogawa T: Pallidoreticular damage in acute carbon monoxide poisoning: diffusion-weighted MR imaging findings: Am J Neuroradiol 2005;26(7):1845–1848.
31 Lam KK, Fung HT, Kam CW: The severity and prognostic markers of 148 cases of carbon monoxide poisoning by burning charcoal: Hong Kong J Emergency Med 2006;13(1):6–16.
32 Rissanen E, Paavilainen T, Virta J, Marttila RJ, Rinne JO, Airas L: Carbon monoxide poisoning-induced nigrostriatal dopaminergic dysfunction detected using positron emission tomography (PET): Neurotoxicology 2010;31(4):403–407.
33 Cardellach F, Garrabou G, Inoriza JM, Martí MJ, Oliu G, López St: Acute carbon monoxide poisoning: treatment with normobaric or hyperbaric oxygen and its correlation with mitochondrial complex IV activity from peripheral blood lymphocytes. Libro de resúmenes, 46th Society of Toxicology (SOT) Annual Meeting, EEUU:,Charlotte,2007.
34 National Health Service: HTA programme: Systematic Review 2 – July 2008. The clinical and cost effectiveness of hyperbaric oxygen therapy: Quality Improvement, Scotland, 2008.
35 Sanders RW, Katz KD, Suyama J, Akhtar J, O'Toole KS, Corll D, Ladenburger RN: Seizure during hyperbaric oxygen therapy for carbon monoxide toxicity: a case series and five-year experience: J Emergency Med 2009; in press, doi:10.1016/j.jemermed.2008.12.017.
36 Weaver LK, Valentine KJ, Hopkins RO: Carbon monoxide poisoning: risk factors for cognitive sequelae and the role of hyperbaric oxygen: Am J Respir Crit Care Med 2007;176(5):491–497.
37 Scheinkestel CD, Bailey M, Myles PS, Jones K, Cooper DJ, Millar IL, Tuxen DV: Hyperbaric or normobaric oxygen for acute carbon monoxide poisoning: a randomised controlled clinical trial: Med J Aust 1999;170(5):203–210.
38 Weaver LK: Hyperbaric oxygen in carbon monoxide poisoning; Letters – Authors of study clarify points that they made: Br Med J 2000;321:109 doi: 10.1136/bmj.321.7253.109.
39 Wolf SJ, Lavonas EJ, Sloan EP, Jagoda AS: Clinical policy: critical issues in the management of adult patients presenting to the emergency department with acute carbon monoxide poisoning: Ann Emergency Med 2008;51(2):138–152.
40 Mathieu D, Nolf M, Durocher A, Saulnier F, Frimat P, Furon D, Wattel F: Acute carbon monoxide poisoning. Risk of late sequelae and treatment by hyperbaric oxygen: J Toxicol Clin Toxicol 1985;23(4–6):315–324.
41 Smith JS, Brandon S: Morbidity from acute carbon monoxide poisoning at three year follow up: Br Med J 1973;1:318–321.
42 Barois, A, Grosbuis S, Goulon M: Les intoxications aiguës par l'oxyde de carbone et les gaz de chauffage: *Rev Prat* 1979;29:1211–1231, cited in WHO (1999).
43 HSE: A review of carbon monoxide incident information for 2003/04, produced from the

full investigation of incidents which had resulted from the use of piped natural gas and LPG within Great Britain, Health and Safety Executive, Research Report 439, HMSO, Norwich, 2006.
44 HSE: A review of carbon monoxide incident information, for 2005/06, produced from the full investigation of incidents which had resulted from the use of piped natural gas and LPG, within Great Britain. Health and Safety Executive, RR634, HMSO, Norwich, 2008.
45 Sánchez BA, Álvarez CC, Álvarez CS: Carbon monoxide intoxication: Puesta al Dia en Urgencias, Emergencias y Catastrofes 2005;6(2):91–98.
46 Huang Y, Liu H, Ho K, Lien F: Carbon monoxide intoxication presented as paroxysmal atrial fibrillation: Acta Cardiologica Sinica 2006;22:45–48.
47 Suner S, Partridge R, Sucov A, Valente J, Chee K, Hughes A, Jay G: Non-invasive pulse CO-oximetry screening in the emergency department identifies occult carbon monoxide toxicity: J Emergency Med 2008;34(4):441–450.
48 UK Department of Health: Accident and emergency attendances, 2009. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Statistics/Performancedataandstatistics/AccidentandEmergency/DH_077485 (accessed September 6, 2009).
49 Basarab M, Leonardi GS, Ruggles R: Developing best practice response to carbon monoxide incidents: a toolkit for health protection frontline staff: Chem Hazards Rep 2008;13:14–17. Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1222068844046.
50 Mandal S, Ruggles R, Murray V, Leonardi G, Goodfellow F, Schweiger M, Bradley N: Developing best practice response to carbon monoxide incidents: a toolkit for health protection frontline staff: Chem Hazards Rep 2008;13:18–21. Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1222068844046.
51 UK CLG: Study of the provision of carbon monoxide detectors under the building regulations, BD 2754, 2009.
52 Croxford B, Hutchinson E, Leonardi GS, McKenna L, Nicholson L, Volans G, Wilkinson P: Real time carbon monoxide measurements from 270 UK homes: Proceedings of the A and WMA Indoor Environmental Quality: Problems, Research and Solutions Conference 2006; 1:400–412.
53 Croxford B: Gas appliance check project: A report on a project funded by the UK Health and Safety Executive, 2006. Available at: www.hse.gov.uk/gas/domestic/uclgasfinal.pdf (accessed September 6, 2006)
54 Croxford B, Leonardi GS, Kreis I: Self-reported neurological symptoms in relation to CO emissions due to problem gas appliance installations in London: a cross-sectional survey: Environ Health 2008;7:34.