UK Health Security Agency

Chronic low-level exposure to hydrogen sulphide and adverse health outcomes

A rapid review

Contents

Main messages

The purpose of this rapid review was to identify and examine evidence on adverse health outcomes of chronic low-level exposure to hydrogen sulphide (H_2S), with a focus on evidence published since the last toxicological report from Public Health England (UKHSA's predecessor). In this context, we summarised 2 systematic reviews with search dates in 2014 (AMSTAR 2 rating: one low quality and one critically low quality). For evidence published after 2014, 15 primary studies were included (search date: 3 October 2023): 3 prospective cohort studies (quality criteria checklist (QCC) rating: medium quality), one time series (QCC rating: medium quality), one time-stratified case-crossover (QCC rating: medium quality), and 10 cross-sectional studies (QCC rating: medium quality for 5 studies, and low quality for 5 studies).

Respiratory outcomes were reported in both systematic reviews and in 9 primary studies, with mixed results in adults (some studies found evidence of an association, and others no evidence of an association) although the better conducted studies (including adjustment for factors such as smoking) did not suggest evidence of an association between adverse long-term respiratory outcomes and chronic low-level exposure to H_2S. For children, whilst evidence from 3 studies suggested that chronic low-level exposure to H_2S may be associated with some adverse respiratory outcomes in children, this was based on very low certainty evidence which limited our ability to draw conclusions (confirmed in a further rapid review in children, search date: 5 June 2024, see supplementary material 2).

Neurological outcomes were reported in both systematic reviews and in 3 primary studies. Overall, results were mixed (some studies found evidence of an association, and others no evidence of an association) although the better conducted studies (including in terms of exposure and outcome assessment) did not suggest evidence of an association between chronic low-level exposure to H_2S and adverse neurological outcomes in adults.

Ocular outcomes in adults were reported in one systematic review, which suggested an association between chronic low-level exposure to H_2S and adverse ocular outcomes, and in 2 primary studies, which found no evidence of an association. However, this was based on a limited number of studies and other factors (such as H_2S odour stimulus and co-exposure to other pollutants) may have impacted the results.

Cardiovascular outcomes were reported in one systematic review and in 5 primary studies, cancer outcomes in one systematic review and in 3 primary studies, and reproductive and developmental outcomes in one systematic review. For all these outcomes, the evidence identified was limited and had important methodological limitations, which limited our ability to draw conclusions.

The evidence identified has important limitations, including in relation to exposure assessment and lack of adjustment for factors that may have affected the results (such as smoking and exposure to other air pollutants). Future research on adverse health effects of chronic, low-level exposure to H_2S should address the methodological limitations identified in this review.

Background

Hydrogen sulphide (H_2S) is a gas that has a distinctive odour referred to as ‘rotten eggs’ (1, 2). Natural environmental sources of H_2S include volcanic gases, geothermal emissions, and breakdown material from plants and animals (3). H_2S is also derived from human activity such as industrial sources including petrochemical refineries, pulp and paper mills, sewage treatment plants, viscose rayon manufacturers, and manure processes (1, 4).

The main route of H_2S exposure is by inhalation (2), with occupational exposure being generally higher than exposure from ambient air (5). Once inhaled, H_2S is rapidly absorbed by the lungs into the bloodstream and widely distributed throughout the body. Hydrogen sulphide is also produced within the body in small amounts, where it is involved in regulating some physiological functions such as vasodilation and neuromodulation (2).

A toxicological overview published in 2016 by Public Health England (PHE) reported that acute exposure to high concentrations of H_2S may result in collapse, respiratory paralysis, cyanosis, convulsions, coma, cardiac arrhythmias, and death within minutes (2). It also found that acute exposure to low concentrations may irritate the eyes and respiratory tract, resulting in sore throat, cough and dyspnoea (2).

In addition, the PHE report suggested that chronic exposure to H_2S may be associated with adverse respiratory, neurological and ocular outcomes, but this was based on limited data. There was also limited data on the impact of chronic exposure to H_2S on reproductive and developmental outcomes such that no conclusions could be drawn (2).

Purpose

The purpose of this work was to identify and assess evidence on the adverse health outcomes of chronic low-level exposure to H_2S in humans. The review question was: ‘What are the adverse health outcomes of chronic low-level exposure to hydrogen sulphide?’

To accelerate the review process, it was agreed by the review team to use review-level evidence to summarise evidence published before the PHE toxicological overview was conducted (2), and primary studies for more recent evidence.

For the purpose of this review, chronic low-level exposure to H_2S was defined as an average exposure below 10 ppm (that is, 14.0 mg/m^3) (6) for one year or more.

Methods

A rapid review was conducted, following streamlined systematic methods to accelerate the review process (7).

Scoping search (systematic reviews)

As part of best practice, a scoping search using PubMed, Google and Epistemonikos (8) was completed by an information scientist on 2 October 2023 to identify any existing reviews (systematic or rapid) related to adverse health outcomes of chronic low-level exposure to H_2S.

The scoping search identified 10 potentially relevant reviews (1 to 3, 5, 9 to 14), of which 2 focused on the adverse health outcomes of chronic low-level exposure to H_2S in humans (3, 5). Both systematic reviews had a search date of 2014, that is, before the PHE toxicological report was published in 2016 (2). Therefore, to accelerate the review process, it was agreed by the review team to summarise these systematic reviews for evidence up to 2014, and to search for primary studies published from 2014 onwards.

Data extraction from the systematic reviews was undertaken by one reviewer and checked by a second.

Critical appraisal was undertaken in duplicate by 2 reviewers using the AMSTAR 2 tool (15). Reviews were given an overall quality rating of high, medium, low, or critically low.

Narrative summaries of the reviews were written by one reviewer and checked by a second. We extracted data from the reviews without undertaking further analysis of the primary studies included in these reviews, although for one of the reviews (3) we reorganised the findings by outcomes rather than by settings.

Review process (primary studies)

A literature search was undertaken by an information scientist using Ovid Medline ALL and Ovid Embase databases to identify primary studies published between 1 January 2014 and 2 October 2023 (search date: 3 October 2023).

Additional sources of evidence included:

- citation searching analysis (backwards, forwards and co-citation) using the included studies as seed papers
- searching the reference lists of potentially relevant reviews identified through the scoping and database searches

The inclusion and exclusion criteria are provided in Table A.1 (Annexe A). Only epidemiological studies (ecological, cohort, case-control and cross-sectional) were considered for inclusion.

The database search results were screened using Rayyan (16). Screening on title and abstract was completed in triplicate by 3 reviewers for 10% of the results and the remaining results were screened by one reviewer. Full-text screening and data extraction were undertaken by one reviewer and checked by a second. Critical appraisal was conducted in duplicate by 2 reviewers, with input from topic advisors as needed. Characteristics of included studies were tabulated, and data combined in a narrative synthesis.

Critical appraisal of the primary studies was conducted in duplicate by 2 reviewers using the quality criteria checklist (QCC) tool (17, 18). Studies were given a quality rating of high, medium or low, which reflects the methodological quality of a study (how well a study was conducted to minimise potential risk of bias). To take into account the risk of bias inherent to different study designs, each study was classified into one of 4 classes based on the hierarchy of evidence (18):

- class A: randomised controlled trials, cluster randomised trials and randomised crossover trials (class A studies were not eligible for inclusion in this review)
- class B: prospective cohort studies and retrospective cohort studies
- class C: non-randomised controlled trials, non-randomised crossover trials, case-crossover studies, case-control studies, time series studies, diagnostic, validity or reliability studies
- class D: non-controlled trials, case studies, case series, other descriptive studies, cross-sectional studies, trend studies, before-after studies

The overall critical appraisal takes into account the study class (or level of evidence) as well as the QCC rating.

Full details of the methodology are provided in Annexe A, with the database search strategies in Annexe B. A protocol was produced a priori and is available on request.

Evidence from systematic reviews

Evidence identified (systematic reviews)

Two systematic reviews that evaluated the adverse health outcomes of chronic low-level exposure to H_2S were identified (3, 5). Details of these 2 reviews can be found in Table S.1 in supplementary material 1 (if this link does not work, please visit UKHSA evidence reviews).

Lewis and Copley conducted a systematic review with narrative synthesis (searches up to February 2014) to assess the evidence on adverse health outcomes of chronic low-level H_2S exposure (defined by review authors as not exceeding an approximate mean of 10 ppm [14.0 mg/m^3]) (5). Health endpoints assessed were respiratory, neurological, ocular, cardiovascular, reproductive and developmental, and cancer. This review, which included 36 primary studies, was rated as low quality using AMSTAR 2, due to the presence of a critical weakness associated with the search strategy. See AMSTAR 2 results in Table C.1 (Annexe C).

Lim and others conducted a systematic review with narrative synthesis (searches up to July 2014) to assess the adverse respiratory and neurological health outcomes of chronic low-level H_2S exposure for studies published between 1980 and 2014 (3). This review, which included 28 primary studies, was rated as critically low quality using AMSTAR 2, mainly due to the presence of a critical flaw associated with the search strategy, as well as the risk of bias assessment being not completely satisfactory. See AMSTAR 2 results in Table C.1 (Annexe C).

To note that 11 primary studies (that reported on respiratory and or neurological outcomes) were included in both systematic reviews (3, 5).

Evidence synthesis (systematic reviews)

Systematic review by Lewis and Copley

The systematic review by Lewis and Copley (AMSTAR 2 quality rating: low), identified 36 studies on the adverse health outcomes of chronic low-level H_2S exposure (22 community-based and 14 occupational-based H_2S exposure) (5). Of the 36 studies, 9 were cohort (6 of which were retrospective, 3 not specified if prospective or retrospective), 3 were case-control studies and 24 were cross-sectional. Twenty-six studies had at least one control group, and 4 studies compared groups with different levels of H_2S exposure. Of the 22 community-based studies, one reported findings for both children and adults, and 4 for children only. Refer to Table S.1 in supplementary material 1 for further details of the systematic review.

Six health outcomes were assessed in the review by Lewis and Copley: respiratory, neurological, ocular, cardiovascular, reproductive and developmental, and cancer; some studies reported on more than one outcome. Summary findings for each outcome are provided below although, due to the way in which findings were summarised, it was not possible to

systematically report some information, such as sample size, exposure dose or comparator groups.

Respiratory outcomes were the most commonly evaluated (23 studies; 15 community-based, 8 occupational) and included self-reported symptoms, asthma, bronchitis, lung function, respiratory infection, hospital admission and mortality (some studies reported on more than one outcome measure). Of the 15 community-based studies, 5 (all cross-sectional, and all with exposure to H_2S emissions from industrial sources), reported findings in children of which 2 found evidence of an association between chronic exposure to air pollutants including H_2S and adverse respiratory outcomes in children. One of the 2 studies found an association for upper respiratory infections in Finnish children under 6 years old living in polluted cities, although the impact of other air pollutants present was not taken into account in the analyses so it is unclear whether the observed association can be attributed to H_2S. In the second study, respiratory symptoms reported by parents of children aged 5 to 13 years old in Canada were associated with chronic total sulphur exposure although the results from lung function tests did not suggest evidence of an association. The review authors concluded that, overall, the evidence available on children did not suggest an association between chronic low-level H_2S exposure and long-lasting adverse respiratory outcomes in children. However, we note this was based on cross-sectional evidence (low-level evidence) with methodological limitations; more studies are needed to confirm these findings.

The findings for respiratory outcomes in adults were mixed, with some studies reporting evidence of an association with chronic low-level exposure to H_2S and others reporting no evidence of an association. Studies which found evidence of an association tended to have important methodological weaknesses (such as self-reported outcomes, selection bias, lack of exposure assessment, and lack of adjustment for factors that may have impacted the results, including co-exposure to other pollutants). The review authors concluded that there was no evidence of long-term, adverse impact of chronic low-level H_2S exposure on respiratory function in adults.

Seventeen studies evaluated neurological outcomes (12 community-based, 5 occupational), which included self-reported symptoms, neurological tests, hospitalisation and mortality, with some reporting on more than one outcome measure. Findings were mixed, with some studies suggesting an association between adverse neurological outcomes and chronic low-level exposure to H_2S, and others reporting no evidence of an association. In particular, self-reported symptoms, such as headaches or fatigue, tended to be reported more frequently in exposed participants (9 studies; one case-control and 8 cross-sectional) although the review authors noted that this could be partly due to the strong odour stimulus associated with exposure and to the lack of consideration of co-exposures to other pollutants in some of the analyses. The 2 studies deemed by review authors to be of higher quality (in terms of outcome and exposure assessment; both cross-sectional) did not suggest an association between adverse neurological outcomes and chronic low-level exposure to H_2S. The only study which reported results for children did not find evidence of an association. However, this study was cross-sectional, outcomes were self-reported and exposure to co-pollutants was not taken into account. The review authors concluded that no conclusion could be drawn for children.

Ten studies reported on ocular outcomes (7 community-based, 3 occupational). Findings were mixed, with some studies reporting evidence of an association and others reporting no evidence of association (including one study in children). However, the review authors concluded that there was some evidence of a positive association between chronic low-level H_2S exposure and hospitalisation for disorders of the eye and adnexa (tissues around the eye) based on 2 studies from Rotorua (New Zealand, geothermal sources of H_2S) which used the same methods but covered different time periods (1981 to 1990, and 1993 to 1996). The review authors advise that these results should be taken with caution due to some limitations of the studies, including lack of adjustment for factors such as smoking and socioeconomic status (results were adjusted for age, race and sex).

The evidence available on cardiovascular outcomes was limited as only 7 studies (5 community-based, 2 occupational) were identified, reporting on a wide range of outcome measures (mortality and hospital discharge data in 4 retrospective cohort studies, self-reported symptoms or prevalence of cardiovascular disease in 2 cross-sectional studies, results of electrocardiogram or echocardiogram investigations in one cross-sectional study). Three of the community-based studies and the 2 occupational studies reported an association between chronic low-level exposure to H_2S and some adverse cardiovascular outcomes. However, all these studies had important methodological limitations, including lack of adjustment for factors that may have impacted the results such as smoking, socio-economic status, and exposure to other pollutants.

The evidence on reproductive and developmental outcomes was limited as only 5 studies (4 community-based, one occupational) were identified. Three of the community-based studies and the occupational study reported on reproductive outcomes with mixed findings but there were important methodological limitations which prevented the review authors from drawing conclusions. Two of the community-based studies reported on developmental outcomes suggesting no evidence of an association, although this was based on limited evidence with methodological limitations.

The evidence on cancer outcomes was limited to 5 studies (4 community-based, one occupational): 3 cohort, one case-control, one cross-sectional. The studies, which considered a range of cancers, provided limited information on H_2S exposure, and findings were based on small numbers of cases, which all limited the review authors' ability to draw conclusions.

Lewis and Copley found that the studies identified had important methodological limitations, including risk of recall bias (mainly due to the potential for H_2S odour to affect recall of self-reported symptoms), lack of adjustment for factors that may have impacted the results (including individual factors such as smoking or socio-economic factors, and co-exposure to other pollutants) and risk of selection bias, including use of convenience samples (for example, plaintiffs in lawsuits which may be non-representative of a population) and lack of information on recruitment of participants. In addition, there were important limitations associated with exposure assessment, whether due to a lack of quantitative data or to the use of population-level data, which may not accurately reflect H_2S exposure at the individual level. Finally, the review authors noted that many (24) of the studies were cross-sectional surveys.

Lewis and Copley concluded that respiratory symptoms were the outcome most associated with exposure to chronic low-level H_2S but that they tended to be temporary and that there was no evidence of impaired lung function in adults or children. The review authors also found that there was some evidence of an association between chronic low-level exposure to H_2S and adverse ocular outcomes in adults, but this was based on limited evidence, and factors not included in the analyses (such as co-exposure to other pollutants and odour stimulus) may have impacted the results. Findings for neurological outcomes were mixed, with some studies reporting an association and others no evidence of an association, although the better-quality evidence available (in terms of outcome and exposure assessment) did not suggest an association between chronic low-level exposure to H_2S and adverse neurological outcomes in adults. Only one study was identified for neurological outcomes in children and no conclusion could be drawn. Finally, the evidence for the other endpoints (cardiovascular, reproductive and developmental, and cancer) was mixed, with some studies suggesting a potential association with chronic low-level H_2S exposure, and others reporting no evidence of an association. However, whilst the review authors concluded that the results for these outcomes "did not indicate a potential health hazard", our assessment of the evidence presented in their review is that it is not possible to draw conclusions for cardiovascular, reproductive and developmental, and cancer outcomes as the evidence available was limited and had important methodological limitations.

Systematic review by Lim and others

The systematic review by Lim and others (AMSTAR 2 quality rating: critically low), identified 28 studies investigating adverse respiratory and or neurological outcomes associated with chronic low-level H_2S exposure (3). Of the 28 studies, 6 were experimental in which H_2S was administered under controlled conditions, and 22 were epidemiological in which H_2S exposure occurred in community-based or industry-based settings (12 and 10 studies respectively). Only the epidemiological studies conducted in community and industrial settings are considered and summarised here because experimental studies of short-term or acute H_2S exposure were out of the scope of this review.

Of the 22 epidemiological studies, 6 were longitudinal and 16 were cross-sectional. Twelve studies had at least one control group. Of the 12 community-based studies, one study reported findings for both children and adults, and one for children only (both reported on respiratory findings only). Refer to Table S.1 in supplementary material 1 for further details of the systematic review.

Respiratory outcomes were assessed in 15 studies (10 community-based, 5 industry-based), neurological outcomes in 12 studies (6 community-based, 6 industry-based), with 6 studies assessing both. Summary findings for each outcome are provided below although, due to the way in which findings were summarised, it was not possible to systematically report some information, such as sample size, exposure dose or comparator groups.

Findings for respiratory outcomes were mixed. Amongst the community-based studies, 5 were conducted in Rotorua, New Zealand (to note that 4 of these 5 studies were also included in

Lewis and Copley's review). The review authors noted that the most recent of these 5 studies, which estimated individual-level exposure (in opposition to previous studies which used population-level exposure), did not find evidence of an association between chronic low-level H_2S exposure and adverse respiratory outcomes in adults. However, 2 longitudinal studies reported an association between chronic low-level H_2S exposure and asthma in adults (prescriptions for anti-asthma in one study assessing day-to-day variations in H_2S exposure, and hospital admission in another study). A third longitudinal (time series) study found an association between day-to-day H_2S emissions and hospital visits for all respiratory diseases, including asthma, in children but not in adults. The other study reporting findings for children (also longitudinal) did not find evidence of an association between day-to-day variations in H_2S exposure and self-reported respiratory symptoms in children. To note that one cross-sectional study (also included in Lewis and Copley's review) reported evidence of an association between chronic low-level H_2S exposure and respiratory diseases in adults, but this was based on self-reported outcomes not adjusted for potential confounders, and the study was at risk of selection bias (convenience sample).

Three of the 5 industry-based studies reported an association between chronic low-level H_2S exposure and respiratory outcomes although these studies used convenience samples (mainly plaintiffs from lawsuits) which limit the confidence in these findings (to note that these studies were not included in the Lewis and Copley review due to these limitations). Of the 2 other studies, one did not find evidence of an association with lung function tests, and one (also included in Lewis and Copley's review) reported an association in non-smoking sewer workers who were also more likely than the comparator group to have obstructive lung function.

For neurological outcomes, findings were also mixed (all cross-sectional studies). Out of the 6 community-based studies (each of which was included in Lewis and Copley's review), 4 were conducted in Rotorua (New Zealand). As for respiratory outcomes, the more recent New Zealand study, which estimated individual-level exposure (in opposition to previous studies which used population-level exposure), did not find evidence of an association between chronic low-level H_2S exposure and adverse neurological outcomes. Similarly, evidence from a well-conducted cross-sectional study in the USA did not report evidence of an association between chronic low-level H_2S exposure (from industrial source) and adverse neurobehavioural outcomes. The last cross-sectional study reported evidence of an association between chronic low-level H_2S exposure and adverse neurological outcomes, but this was based on self-reported outcomes not adjusted for potential confounders, and the study was at risk of selection bias (convenience sample).

Four of the 6 industry-based studies reporting on neurological outcomes found a positive association with chronic low-level H_2S exposure studies but, as for the respiratory outcomes, confidence in these findings was limited due to the use of convenience samples (one of these 4 studies was included in the Lewis and Copley review). Another cross-sectional study (included in Lewis and Copley's review) also suggested evidence of an association, but it was noted that the sewer workers in this study were exposed to other chemicals which may have impacted the findings. The last study (also included in Lewis and Copley's review), which was well-conducted, did not find evidence of an association.

Lim and others noted that there was limited evidence available for these outcomes, and that there were important differences between the studies identified in terms of study design, populations, sample sizes, and settings. They also reported that drawing conclusions from the evidence was challenging because of methodological differences and methodological limitations of the studies, including co-exposure to other chemicals, lack of adjustment for factors that may have impacted the results, and use of convenience samples of plaintiffs in lawsuits with known adverse health outcomes.

Lim and others concluded that based on the best evidence available (in terms of methodological quality), there was no evidence of adverse respiratory and neurological outcomes associated with chronic low-level exposure to H_2S, although there was some evidence of an association between day-to-day variation of H_2S levels and asthma in both children and adults.

Summary findings (systematic reviews)

Respiratory and neurological outcomes were reported in the 2 systematic reviews identified. There was some evidence that respiratory symptoms in adults were associated with exposure to chronic low-level H_2S but they tended to be temporary and the best evidence available (in terms of methodological quality) did not suggest evidence of adverse long-term respiratory outcomes associated with chronic low-level exposure to H_2S (3, 5). However, there was limited evidence suggesting that there may be an association between day-to-day variation of H_2S levels and asthma in both children and adults (3). Regarding findings in children specifically, as there was no overlap of primary studies reporting on respiratory outcomes in children between the 2 systematic reviews (the reviews included different primary studies) our confidence that all relevant studies published before 2014 were identified is limited.

Findings for neurological outcomes were mixed, with some studies reporting an association and others no evidence of an association, although the better quality studies (in terms of outcome and exposure assessment) did not suggest evidence of an association between chronic low-level exposure to H_2S and adverse neurological outcomes in adults (3, 5). Only one study was identified for neurological outcomes in children and no conclusion could be drawn. To note that this body of evidence was mainly based on cross-sectional studies (therefore providing low-level evidence) and that there was an important overlap in primary studies between the 2 reviews.

Other adverse health outcomes (ocular, cardiovascular, reproductive and developmental, and cancer) were reported in only one of the reviews (5). For ocular outcomes, there was some evidence suggesting an association between chronic low-level exposure to H_2S and adverse ocular outcomes in adults, although this was based on a limited number of studies and other factors, such as co-exposure to other pollutants and odour stimulus, may have impacted the results (5). One study had reported ocular outcomes in children and found no evidence of an association.

The evidence identified for cardiovascular, cancer, and reproductive and developmental outcomes was mixed, with some studies reporting an association between exposure and

outcome, and others reporting no evidence of an association (5). However, this was based on limited evidence with important methodological limitations, and it was not possible to draw conclusions for cardiovascular, reproductive and developmental, and cancer outcomes (5)

Overall, the studies identified in these 2 systematic reviews had important methodological limitations, including use of non-representative samples (such as convenience samples), inadequate H_2S exposure assessment (in particular, lack of quantitative data and population-level assessment), self-reported outcomes (which may have been impacted by participants' ability to smell H_2S), and lack of consideration of other factors which may have impacted the results (such as smoking or co-exposure to other pollutants). In addition, there were differences in methodologies and settings between studies which impacted the review authors' ability to synthesise findings and draw conclusions.

Evidence from primary studies

Search results (primary studies)

The database search for primary studies returned 4,061 records. After removal of duplicates using Deduklick (19) and Rayyan (16), 2,572 records were screened on title and abstract. Of these, 66 full-text articles were assessed for eligibility and 15 were included in this review.

These 15 studies were used as seed papers for citation searching; this identified a further 388 records. These 388 records were screened on title and abstract. Of these, one full-text article was assessed for eligibility and was excluded.

Searching the reference lists of potentially relevant reviews (4 identified during the scoping search and 9 from the database searches) (1, 3, 4, 5, 10, 20, 21, 22, 23, 24, 25, 26, 27) identified one unique primary study, which was assessed for eligibility on full-text screening and was excluded.

In total, 15 primary studies were included in this review. A Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram is provided in Figure A.1 (Annexe A).

A summary of the included studies can be found in Table 1 and Table 2, with further details in Tables S.2 and S.3 in supplementary material 1 (if these links do not work, please visit UKHSA evidence reviews).

The 53 reports excluded on full text can be found in Tables S.4 to S.8 in supplementary material 1, listed by reason for exclusion.

Evidence identified (primary studies)

Of the 15 studies identified, 5 studies were longitudinal: 3 prospective cohort studies (study design class B; QCC rating: medium quality) (28, 29, 30), one time series (study design class C; QCC rating: medium quality) (31) and one time-stratified case-crossover study, where cases served as their own controls (study design class C; QCC rating: medium quality) (32). The remaining 10 studies were cross-sectional (study design class D; QCC rating medium quality for 5 studies (33 to 37) and low quality for 5 studies (38, 39, 40, 41, 42)). See QCC results in Table C.2 (Annexe C).

Out of the 15 studies, 3 were linked studies (part of the same wider study) conducted in Rotorua city in New Zealand (33, 34, 35) and 2 were linked studies conducted in sewage-treatment plants in Norway (36, 37). There were also 2 studies conducted in Reykjavik in Iceland reporting on the same population but not linked (31, 32). Three studies were conducted in Italy (but in different populations) (28, 29, 30) and one each in China (42), Indonesia (38), Malaysia (40), Iran (41) and Syria (39).

Ten studies were conducted in community settings in which local populations were exposed to chronic low-level H_2S from geothermal sources (6 studies (30, 31, 32, 33, 34, 35)) or from landfill sites (4 studies (28, 29, 38, 42)). Five studies were conducted in occupational settings: 3 in sewage workers (36, 37, 40) and 2 in workers from petrochemical facilities (39, 41).

Ten of the 15 studies aimed to assess adverse health outcomes associated with H_2S exposure specifically (28, 30, 31, 33, 34, 35, 36, 38, 39, 41), and 5 studies assessed the outcomes from exposure to a range of pollutants, including H_2S (29, 32, 37, 40, 42).

Outcomes assessed included morbidity and mortality measures for a range of health conditions such as cardiovascular, respiratory, ocular, neurological and cancer. Two of the 15 studies reported on biomarkers rather than health outcomes, including haematological parameters (41) and liver enzymes (39).

H_2S exposure levels were reported using a variety of units in the primary studies: milligrams per cubic metre (mg/m^3), micrograms per cubic metre (mcg/m^3), nanograms per cubic metre (ng/m^3), parts per million (ppm) and parts per billion (ppb). In the following summary of evidence, H_2S exposure levels are reported using the same units as those used in the included studies, with corresponding values in mg/m^3 and ppm shown in square brackets based on the conversion 1.40 mg/m^3 = 1 ppm (6).

Evidence synthesis (primary studies)

Community settings

Out of the 10 studies conducted in community settings, 3 were prospective cohort studies (study design class B) rated as medium quality (28, 29, 30). All 3 were conducted in Italy but in different populations, with sample sizes ranging from 33,804 to 242,409 participants, maximum follow-up time from 9 to 16 years, and mean H_2S exposure from 0.006 to 7 mcg/m^3 [0.000006 to 0.007 mg/m^3; 0.000005 to 0.005 ppm]. There were 2 studies from Iceland (one time series and one time-stratified case-crossover study, both study design class C and rated as medium quality), which had a duration of 7 years, with mean exposure to H_2S between 3 and 4 mcg/m^3 [0.003 and 0.004 mg/m^3; 0.002 and 0.003 ppm], and number of events ranging from 10,712 (deaths) to 32,961 (hospital visits) (31, 32). The remaining 5 studies were cross-sectional (study design class D; 3 rated as medium quality (33, 34, 35), and 2 as low quality (38, 42)) and included between 100 and 1,637 participants chronically exposed to H_2S levels (for up to 30 years in one study) of between 2.4 and 90 mcg/m^3 [0.002 and 0.090 mg/m^3; 0.002 and 0.064 ppm]. See Table 1 for a summary of the studies, and Table S.2 in supplementary material 1 for further details.

Mataloni and others conducted a prospective cohort study (study design class B; rated as medium quality) in the Lazio region (Italy) to assess the association between exposure to H_2S from 9 municipal waste landfills and cardiovascular or respiratory hospitalisations and mortality (mean annual exposure for the whole sample: 6.3 ng/m^3 [0.000006 mg/m^3; 0.000005 ppm], standard deviation (SD): 22.5 ng/m^3 [0.00002 mg/m^3; 0.00002 ppm]; mean annual exposure for

those living near to the 2 largest landfills: 32.7 and 45.8 ng/m^3 [0.00003 and 0.00005 mg/m^3; 0.00002 and 0.00003 ppm]) (28). The study, conducted between 1996 and 2012, included 242,409 participants (adults and children) with a follow-up time of up to 11 years for mortality and 16 years for hospitalisation. Findings (Cox model) suggested an association between chronic low-level exposure to H_2S and increased rates of hospitalisation for respiratory disease (which includes acute respiratory infections, and asthma) in adults and children combined (hazard ratio [HR] 1.02, 95% confidence interval [CI] 1.00 to 1.03) and in children aged 0 to 14 years (HR 1.04, 95% CI 1.01 to 1.07). In children, the findings also suggested an increased rate of hospitalisation for acute respiratory infections (HR 1.06, 95% CI 1.02 to 1.11) but not for hospitalisations for asthma specifically (HR 1.07, 95% CI 0.99 to 1.14). No evidence of an association was found for hospitalisation for cardiovascular disease (CVD) in adults and children combined. There was also evidence of increased rates of lung cancer mortality (HR 1.10, 95% CI 1.02 to 1.19) and respiratory disease mortality (HR 1.09, 95% CI 1.00 to 1.19), but not for other mortality outcomes (including 9 other cancers, CVD, digestive diseases and urinary system diseases) (28). This was an open cohort, and although the Cox model accounts for differences in duration of follow up, follow-up durations varied widely, from 5 to 11 years for mortality and from 4 to 16 years for hospitalisation. It should also be noted that exposure to H_2S was based on a dispersion model and participants were assigned one exposure value for the duration of the study. In addition, whilst the model was adjusted for a range of confounding factors such as socio-economic status, particulate matter 10 (PM_{10}) background concentration and whether participants lived near to a road or to an industrial plant, other potential confounders, such as smoking, were not accounted for.

Ancona and others conducted a prospective cohort study (study design class B; rated as medium quality) in Italy to assess the association between living near sources of air pollution (H_2S, sulphur oxides [SO_x] and PM_{10} from landfill, medical waste incinerator and petrochemical refinery) and morbidity and mortality outcomes (29). A total of 85,559 residents (adults and children) were included with a follow-up period of 9 years (2001 to 2010, closed cohort). The mean annual exposure to H_2S from the landfill was 0.02 mcg/m^3 [0.00002 mg/m^3; 0.00001 ppm], SD 0.03 mcg/m^3 [0.00003 mg/m^3; 0.00002 ppm]. Analyses (Cox model) showed that H_2S exposure was associated with an increased rate of CVD hospitalisation in females (HR 1.04, 95% CI 1.00 to 1.09), but not for males and not for CVD mortality in either sex. H_2S exposure was also associated with increased rates of hospitalisation for laryngeal cancer (HR 1.36, 95% CI 1.08 to 1.72), laryngeal cancer mortality (HR 1.36, 95% CI 1.02 to 1.83), and bladder cancer mortality (HR 1.35, 95% CI 1.00 to 1.82) in females, although the mortality data were based on a small number of cases (6 and 12, respectively) and the confidence intervals were wide, indicating uncertainty in the results. There was no evidence of an association for hospitalisation or mortality for respiratory diseases for males or females (29). The results were adjusted for confounders such as socio-economic status and nitrogen dioxide (NO_2) concentrations, but not for other potential confounders such as smoking or alcohol consumption. H_2S exposure was estimated based on the Landfill Gas Emissions model, and it was assumed that the exposure levels were constant throughout the study. Finally, bi-pollutant analyses were conducted to take into account that the study had also assessed the potential adverse health outcomes associated

with exposure to SO_x and PM_{10}. However, the analysis for H_2S exposure and health outcomes was mainly conducted using a single-pollutant model.

The prospective cohort study conducted by Nuvolone and others (study design class B; rated as medium quality) included 33,804 participants (children and adults) living in 6 municipalities near geothermal power plants in Mount Amiata in Italy (30). The study ran from 1998 to 2016 (391,002 person-years) and investigated the association between chronic low-level H_2S exposure (mean 7.0 mcg/m^3 [0.007 mg/m^3; 0.005 ppm], SD 7.2 [0.007 mg/m^3; 0.005 ppm], range 0.5 to 33.5 mcg/m^3 [0.0005 to 0.03 mg/m^3; 0.0004 to 0.02 ppm]) and mortality or hospitalisation from neoplasms, cardiorespiratory or nervous system disorders. Duration of follow up was up to 19 and 17 years respectively for hospital discharge and mortality data relating to neoplasms, and up to 14 years for the other disease groups (open dynamic cohort with differences in follow-up duration, but variation in follow-up not reported). Analyses (Cox model) showed that chronic low-level exposure to H_2S was associated with an increased rate of diseases of the respiratory system (for mortality but not for hospitalisation), with evidence of an exposure-related trend (increased rates as exposure increased). Findings for hospitalisation and mortality for individual respiratory diseases were inconsistent. See Table S.2 (supplementary material 1) for further details. There was evidence that chronic low-level H_2S exposure was associated with an increased rate of hospitalisation for neurological and cardiovascular diseases (disorders of the nervous system and sense organs, and diseases of the circulatory system respectively), but no evidence of an association was found for mortality. Findings for hospitalisation and mortality for individual diseases of the circulatory system were inconsistent. No evidence of an association was found between H_2S exposure and hospitalisation for disorders of the eye and adnexa. There was evidence that chronic low-level H_2S exposure was associated with reduced rates of mortality and hospitalisation for the overall category all neoplasms but there were no statistically significant associations found for individual cancers (except for a positive association between chronic low-level H_2S exposure and hospitalisation for malignant neoplasm of the ovary). However, it should be noted that the study assessed many outcomes and there was no adjustment for conducting multiple statistical tests, which may have increased the likelihood of detecting spurious associations. In addition, inconsistencies in findings between hospitalisation and mortality may be due to the smaller number of deaths for some outcomes, and it is unclear how the competing risk of mortality from other causes was accounted for in the analysis of cause-specific mortality. H_2S exposure was estimated based on a dispersion model, and participants were assigned one exposure value for the duration of the study. Finally, whilst results were adjusted for gender and socio-economic status (more than half of the participants were of high socio-economic status, which was associated with lower H_2S exposure), they were not adjusted for individual factors, such as smoking, diet, alcohol or physical activity, or other environmental factors which may have impacted the results.

Table 1. Summary table – primary studies in community settings

Reference	Study design and follow-up duration	Number of participants	H_2S exposure level	Confounders adjusted for	Main findings
Ancona and others, 2015 (29) QCC rating: medium quality (study design class B)	Prospective cohort Follow-up duration: 9 years	n=85,559	Mean annual exposure 0.00001 ppm, SD 0.00002 ppm	• Area-based socio-economic index • Outdoor NO_2 concentrations • Education • Employment • Relationship status	Hospitalisation: • for CVD disease in females: HR 1.04, 95% CI 1.00 to 1.09 • for laryngeal cancer in females: HR 1.36, 95% CI 1.08 to 1.72 All-cause and cause-specific mortality: • mortality from laryngeal cancer in females (6 cases only): HR 1.36, 95% CI 1.02 to 1.83 • mortality from bladder cancer in females (12 cases only): HR 1.35, 95% CI 1.00 to 1.82 No evidence of an association in males or females for the other outcomes assessed (diseases of the cardiovascular, respiratory, digestive, or genitourinary systems, and cancer; see Table S.2 in supplementary material 1 for full details)
Bates and others, 2015 (34) QCC rating: medium quality (study design class D)	Cross-sectional	n=1,204	Exposure range estimate between 0 ppm and 0.06 ppm	• Smoking • Education level • Income level • Self-identified Polynesian ethnicity	No evidence of an association between H_2S exposure and: • asthma (assessed on spirometry or on self-reported diagnosis) • chronic obstructive pulmonary disease (assessed on spirometry) • lung function tests (FVC, FEV_1, FEF, FEV_1 to FVC ratio)
Bates and others, 2017 (33) QCC rating: medium quality (study design class D)	Cross-sectional	n=1,637	Not reported	• Age • Smoking	No evidence of an association between H_2S exposure and: • any Lens Opacity Classification System (LOCS III) scores (nuclear opacity, nuclear colour, cortical, posterior subcapsular) • cataract (LOCS III score of 2 or more)
Finnbjornsdottir and others, 2015 (32) QCC rating: medium quality	Time-stratified case-crossover Study period January 2003	n=7,679 all natural cases deaths, n=3,033 cardiovascular related deaths	Mean exposure 0.002 ppm (SD 0.005 ppm)	• Temperature • Humidity	All cause natural mortality: • short-term increases in concentration of H_2S (0.002 ppm) associated with increased risk of death during summer months at 1 and 2 days after peak exposure • increased risk of death among males on the day of the peak exposure • increased risk of death for those aged 80 years or older on the day of the peak exposure and one day later

Reference	Study design and follow-up duration	Number of participants	H_2S exposure level	Confounders adjusted for	Main findings
(study design class C)	to December 2009				• increased risk of death with H_2S level exceeding 0.005 ppm in summer months at 2 and 3 days after the peak exposure See Table S.2 (supplementary material 1) for further details. Cardiovascular mortality: • no evidence of an association with H_2S exposure
Finnbjornsdottir and others, 2016 (31) QCC rating: medium quality (study design class C)	Longitudinal time series Study period June 2007 to June 2014	n=13,383 patients, n=32,961 emergency hospital visits	Mean exposure between 0.002 ppm and 0.003 ppm	• Sex • Age • Seasonality • Traffic exposure • Distance from geothermal power plant • Temperature	Association between H_2S exposure over 0.005ppm and emergency hospital visits for: • heart disease on the day of the peak exposure (RR 1.07, 95% CI 1.02 to 1.11), 2 days later (RR 1.05, 95% CI 1.01 to 1.10) and 4 days later (RR 1.05, 95% CI 1.00 to 1.09) • stroke in patients over 73 years old 2 days after peak exposure (RR 1.14, 95% CI 1.00 to 1.29) No evidence of an association found between H_2S exposure over 0.005 ppm and emergency hospital visits for respiratory diseases
Hidayati and others, 2020 (38) QCC rating: low quality (study design class D)	Cross-sectional	n=100	0.01 ppm (unclear if mean value)	No statistical analysis	Self-reported respiratory symptoms reported by 81% of participants
Mataloni and others, 2016 (28) QCC rating: medium quality (study design class B)	Prospective cohort Follow-up duration: from 5 to 11 years for mortality, 4 to 16 years for hospitalisation	n=242,409	Mean annual exposure 0.000005 ppm, SD 0.00002 ppm	• Socio-economic status • PM_{10} background concentration • Living near a road or an industrial plant	Hospitalisation: • respiratory disease in adults and children: HR 1.02, 95% CI 1.00 to 1.03 • respiratory disease in children: HR 1.04, 95% CI 1.01 to 1.07 • acute respiratory infections in children: HR 1.06, 95% CI 1.02 to 1.11 Mortality: • lung cancer: HR 1.10, 95% CI 1.02 to 1.19 • respiratory disease: HR 1.09, 95% CI 1.00 to 1.19 No statistically significant association: • hospitalisation for CVD • other mortality outcomes
Nuvolone and others, 2019 (30)	Prospective cohort	n=33,804	Mean 0.005 ppm, SD 0.005 ppm	• Sex	Hospitalisation: • increased rate of pneumonia, chronic obstructive pulmonary disease, disorders of the nervous system and sense organs, disorders of the peripheral nervous system,

Reference	Study design and follow-up duration	Number of participants	H_2S exposure level	Confounders adjusted for	Main findings
QCC rating: medium quality (study design class B)	Follow-up duration: up to 14 years for hospitalisation and mortality (except for neoplasms: up to 19 years for hospitalisation and 17 years for mortality)			• Socio-economic status	diseases of the circulatory system, heart failure, diseases of the veins and lymphatics • reduced rate for 'other respiratory diseases' (diseases not specified), 'all malignant neoplasms', and cerebrovascular diseases • no evidence of an association for disorders of the eye and adnexa Mortality: • increased rate for all respiratory diseases, and pneumonia • reduced rate for non-accidental mortality and mortality from 'all malignant neoplasms', acute myocardial infarction, ischaemic heart disease See Table S.2 (supplementary material 1) for further details.
Pope and others, 2017 (35) QCC rating: medium quality (study design class D)	Cross-sectional	n=1,635	Exposure range estimate between 0 ppm and 0.06 ppm	• Age • Ethnicity • Sex • Diabetes • Smoking	No evidence of an association between H_2S exposure and any of 5 indicators of peripheral neuropathy, or the neuropathy composite index score
Yu and others, 2018 (42) QCC rating: low quality (study design class D)	Cross-sectional	n=951	Means for 4 exposed schools ranging from 0.002 ppm (SD 0.001 ppm) to 0.004 ppm (SD 0.0008 ppm). Mean for comparison school 0.001 ppm (SD 0.00006)	• Age • Sex • BMI • Smokers at home • Pets at home • Coal use at home • Living close to main road	H_2S exposure associated with reductions in: • lung function tests FEV_1, MMF, MVV, FEF_{25}, FEF_{50}, FEF_{75} • salivary IgA levels No evidence of an association between H_2S exposure and lysozyme levels

Acronyms: CI = confidence interval, CVD = cardiovascular disease, FEV_1 = forced expiratory volume in one second, $FEF_{25\ to\ 75}$ = forced expiratory flow 25% to 75% (the mean rate of flow for the middle part of the FVC test, FVC = forced vital capacity, HR = hazard ratio, H_2S = hydrogen sulphide, IgA = immunoglobulin A, LOCS = lens opacity classification system, MMF = mean forced expiratory flow, MVV = maximum voluntary ventilation, n = number, NO_2 = nitrogen dioxide, PM_{10} = particulate matter 10, ppm = parts per million, QCC = quality criteria checklist, RR = relative risk, SD = standard deviation

Two studies were conducted in Reykjavik in Iceland where the population is continuously exposed to H_2S from a geothermal powerplant (31, 32). The mean exposure to H_2S was between 3.0 and 4.0 mcg/m^3 [0.003 and 0.004 mg/m^3; 0.002 and 0.003 ppm], and both studies looked at the short-term associations between exposure exceeding 7 mcg/m^3 [0.007 mg/m^3; 0.005 ppm] ('peak exposure') and outcomes. One of the studies was a time-stratified case-crossover study (study design class C; rated as medium quality) that reported on mortality from all natural causes and cardiovascular diseases (7,679 and 3,033 deaths, respectively), over a 7-year period (32). In this study, the authors also assessed the association between traffic-related pollutants and mortality (PM_{10}, NO_2 and SO_2; results not reported here as out of scope of this rapid review) and both single pollutant and multivariate analyses were performed to account for possible correlation between pollutants. H_2S exposure was based on ambient levels measured at one station in the city. Analyses (logistic regression) found no evidence of an association between low-level H_2S exposure and cardiovascular mortality, both in the single pollutant and multivariate analyses, as well as when stratified by season, age (younger or older than 80 years old), and sex. There was a pattern of association between H_2S exposure and all natural cause mortality that was not observed for the other pollutants: in the summer months, increases in H_2S concentrations of 2.6 mcg/m^3 [0.003 mg/m^3; 0.002 ppm] were associated with increased risk of all natural cause mortality one and 2 days after exposure, but not during the winter months. Analysed by age and sex, the risk of all natural cause mortality increased on the day of peak exposure in males (but not in females), and on the day of peak exposure and one day later for individuals age 80 years and above. Additionally, in the summer months results suggested that H_2S exposure levels exceeding 7 mcg/m^3 [0.007 mg/m^3; 0.005 ppm] increased the risk of all natural cause mortality 2 and 3 days later (refer to Table S.2 in supplementary material 1 for further details) (32).

The second study from Iceland was a longitudinal time series (study design class C; rated as medium quality) that reported on emergency hospital visits (32,961 hospital visits over a 7-year period) (31). Participants were assigned a level of H_2S exposure based on dispersion modelling and depending on the city section in which they lived. The results suggested that H_2S exposure over 7 mcg/m^3 [0.007 mg/m^3; 0.005 ppm] was associated with an increased risk of emergency hospital visits for heart disease on the day of the peak exposure (RR 1.07, 95% CI 1.02 to 1.11), 2 days later (RR 1.05, 95% CI 1.01 to 1.10) and 4 days later (RR 1.05, 95% CI 1.00 to 1.09), and for stroke in participants over 73 years old 2 days after peak exposure (RR 1.14, 95% CI 1.00 to 1.29). There was no evidence of an association for respiratory diseases (31). Adjustment for factors such as traffic exposure zone, traffic related pollutants (PM_{10}, NO_2 and SO_2 and ozone), sex, age and seasonality did not modify the associations observed. However, additional factors that may have impacted the results, such as socio-economic status or smoking, were not taken into account in the analyses.

The remaining 5 studies conducted in community settings were all cross-sectional. Of these, 3 reported on the same population group from Rotorua city (up to 1,637 adults) in New Zealand (study design class D; all 3 studies rated as medium quality) and assessed different outcomes at one point in time, between 2008 and 2010 (33-35). In these studies, the range of exposure to H_2S from geothermal sources was estimated to be between 0 and 0.09 mg/m^3 [0 and 0.06ppm]

over the previous 30 years. However, this exposure assessment may not accurately reflect the exposure over the previous 30 years as it was based on a total of 6 weeks of measurements between 2010 and 2011, and therefore is unlikely to have taken into account changes over time or variations due to meteorological conditions and seasonality. In addition, the studies are limited by selection bias as participants in these studies were not representative of the population invited to participate (33, 34, 35). Results were adjusted for a range of factors, including smoking status, and there was no evidence of an association between chronic low-level H_2S exposure and chronic obstructive pulmonary disease (COPD) or asthma (34), ocular outcomes (33), or peripheral neuropathy outcomes (35).

One cross-sectional study, conducted in China (study design class D; rated as low quality), included 951 children from 5 schools (mean age 10 years old) and compared lung function in children exposed to 7 air pollutants from landfill, including H_2S, (4 schools between 0.8km and 3.4km from a municipal solid waste landfill, exposed schools) with children from one school further away (5.8km) from the landfill (comparison school). In the 4 exposed schools, mean exposure to H_2S ranged from 2.4 mcg/m^3 to 4.9 mcg/m^3 [0.002 mg/m^3 to 0.005 mg/m^3; 0.002 ppm to 0.004 ppm], SDs 1.8 mcg/m^3 [0.002 mg/m^3; 0.001 ppm] and 1.1 mcg/m^3 [0.001 mg/m^3; 0.0008 ppm] respectively. In the comparison school, the mean H_2S exposure was 1.6 mcg/m^3 [0.002 mg/m^3; 0.001 ppm], SD 0.09 mcg/m^3 [0.00009 mg/m^3; 0.00006 ppm] (42). Chronic low-level H_2S exposure was associated with reduced non-specific immunity and lung function (adjusted for sex, age, body mass index (BMI) and whether there were smokers at home). Of the 7 air pollutants assessed in the study, sulphur dioxide was most robustly associated with lung function, followed by H_2S. Multi-pollutant regression models were conducted, and results suggested that the associations between exposure to H_2S and health outcomes were not sensitive to the other pollutants. However other factors not taken into account in the analyses may have impacted the results, including the children's socio-economic status and lifestyle factors such as physical activity. It is also unclear whether all children in the schools were included in the study, or whether there were any further differences between schools.

The final cross-sectional study (study design class D; rated as low quality) was conducted in Indonesia and included 100 participants living near a landfill site (H_2S levels of 0.02 mg/m^3 [0.01 ppm]), of which 81% reported having experienced respiratory problems (38). However, it is unclear how participants were selected, outcomes were self-reported, and findings were not adjusted for potential confounding factors.

Summary findings – community settings (primary studies)

Respiratory outcomes were reported in 7 studies: 3 prospective cohort (study design class B) rated as medium quality (28, 29, 30), one time series (study design class C) rated as medium quality (31), and 3 cross-sectional studies (study design class D), one of which rated as medium quality (34) and 2 as low quality (38, 42). Results were mixed, with some studies reporting that chronic low-level H_2S exposure may be associated with an increased risk of respiratory diseases (based on hospitalisation, mortality data, lung function tests and self-reported symptoms) and others reporting no evidence of an association. The only study (cross-sectional)

conducted in adults which accounted for the potential impact of smoking found no evidence of association between H_2S exposure and lung function, asthma and COPD (34). Both studies that reported results for children found evidence that chronic low-level H_2S exposure may be associated with some adverse respiratory outcomes in children, although factors not included in the analyses may have impacted the results (including individual factors and co-exposure to other air pollutants) (28, 42). Another important limitation is that due to the study design (cross-sectional) or outcome assessed (hospitalisation), none of the studies identified assessed long-term outcomes from chronic low-level exposure to H_2S. Therefore, this body of evidence is based on outcomes assessed in the short-term (for instance, hospitalisation for respiratory infection), or on a single assessment of lung function.

Cardiovascular outcomes were reported in 5 studies: 3 prospective cohort (study design class B) rated as medium quality (28, 29, 30), one time series (study design class C) and one time-stratified case-crossover study (study design class C), both rated as medium quality (31, 32). Findings were mixed across studies: one cohort study reported no evidence of association between H_2S exposure and CVD hospitalisation or mortality (28). Another cohort study also found no evidence suggesting an association between H_2S exposure and CVD mortality, but there was evidence suggesting an association with increased rate for CVD hospitalisation in females but not in males (29). In the third cohort study, findings for cardiovascular outcomes were inconsistent for hospitalisation and mortality across the range of cardiovascular disease categories assessed (30). Whilst the 3 prospective cohort studies included both adults and children, cardiovascular outcomes were not reported separately for children (28, 29, 30). The time-series study found evidence suggesting that chronic low-level H_2S exposure may be associated with emergency hospital visits due to heart disease regardless of age, and for stroke in patients over 73 years old (31). The time-stratified case-crossover study found no evidence suggesting an association between H_2S exposure and cardiovascular mortality (32). All of these studies had adjusted for some confounding factors, but not for lifestyle factors such as smoking, alcohol consumption or physical activity, which may have impacted the results.

Three prospective cohort studies (study design class B; all 3 rated as medium quality) reported on cancer outcomes; whilst the 3 included both adults and children, outcomes were not reported separately for children (28, 29, 30). No conclusions could be drawn from the findings as the studies reported on a range of different cancers, and none of the studies adjusted for individual factors which may have impacted the results, such as smoking, diet, alcohol or physical activity.

Two studies reported on neurological outcomes: one prospective cohort (study design class B; rated as medium quality) which reported that chronic low-level exposure to H_2S may be associated with hospitalisation for disorders of the nervous system (30), and one cross-sectional (study design class D; rated as medium quality) which had adjusted for further potential confounders (including ethnicity and smoking) and did not find evidence of an association with peripheral neuropathy outcomes (35).

Ocular outcomes were reported in 2 studies: one prospective cohort (30) (study design class B) and one cross-sectional (33) (study design class D) both rated as medium quality. No evidence suggesting an association between chronic low-level H_2S exposure and hospitalisation for

disorders of the eye and adnexa, or eye lens changes was identified, however only one study adjusted for factors that might have impacted the results.

The main limitation of this body of evidence is that factors that may have impacted the health outcomes assessed, such as alcohol consumption and physical activity, were not accounted for in the analyses, and smoking was accounted for in only 4 out of 10 studies. In addition, the studies were conducted in settings in which other air pollutants were likely to have been present which may have impacted the results. Whilst some studies attempted to take co-exposure to other air pollutants into account, the different pollutant levels are likely to be dependent on each other which may have affected the ability of the researchers to identify the impact of individual pollutants.

Another important limitation is related to H_2S exposure assessment. Across the studies, different methods were used to assess H_2S exposure levels, including ambient air monitoring (providing a population-level exposure measurement) and dispersion modelling (an indirect method to estimate average individual exposure at population-level). There were differences across studies in how the dispersion modelling was conducted and reported, including whether meteorological conditions and seasonality were taken into account. Therefore, the H_2S exposure levels assigned may not accurately reflect the level of exposure that individuals experienced, which may have impacted the results.

Workplace settings

Five cross-sectional studies (study design class D; 2 rated as medium quality (36, 37) and 3 rated as low quality (39, 40, 41)) reported on the association between low-level occupational H_2S exposure and adverse health outcomes. See Table 2 for a summary of the studies, and Table S.3 in supplementary material 1 for further details.

Two of these studies were linked cross-sectional studies (study design class D; both rated as medium quality), conducted among wastewater workers in Norway. One study assessed neuropsychological motor function in 138 workers in 2013 (112 exposed to H_2S and 26 unexposed) (36). The other study assessed the impact of exposure to H_2S, endotoxin and particle dust on respiratory function in 148 workers in 2015 (121 currently exposed to sewage and 27 with no or little exposure); results for endotoxin and particle dust exposure not reported here as out of scope of this rapid review (37). It is unclear whether there was overlap between the participants in these 2 studies. In both studies, participants' typical workplace H_2S exposure was estimated based on measured peaks above 0.1 ppm, 1 ppm, 5 ppm and 10 ppm [0.1 mg/m^3, 1.4 mg/m^3, 7.0 mg/m^3, 14.0 mg/m^3] and the duration of the peaks. In the analysis of motor function, simple reaction time and one of 6 body sway parameters (intensity) with eyes open were higher in the exposed group than the unexposed group. However, there was no evidence of dose-response when comparing groups by H_2S exposure levels and no evidence of association for hand co-ordination, other body sway parameters with eyes open, or any body sway parameter with eyes blindfolded (36). There was an association between long-term exposure to H_2S and reduced balance (sway velocity) among smokers but other factors not taken into account in the analysis may have contributed to this finding (36). In addition, the

clinical relevance of these findings is unclear and was not addressed in the study. There was no evidence of associations between H_2S exposure and respiratory outcomes in the study that also assessed the impact of exposure to endotoxin and particle dust (results were adjusted for factors such as smoking and BMI) (37).

A cross-sectional study conducted in 191 sewage workers in Malaysia in 2021 (study design class D; rated as low quality) aimed to assess the association between respiratory symptoms and ambient exposure to H_2S (mean 2.4 mg/m^3 [1.7 ppm], mean employment duration 5.4 years) and particulate matter (40). Individual cumulative exposure to H_2S was positively associated with the presence of respiratory symptoms (adjusted odds ratio [OR] 1.04, 95% CI 1.01 to 1.07). However, respiratory symptoms were self-reported, and it is unclear whether the analysis adjusted for other factors that could have impacted the results.

The remaining 2 cross-sectional studies were conducted in petrochemical workers, focusing on changes to blood markers associated with ambient H_2S exposure. Saeedi and others (study design class D; rated as low quality) found no evidence of differences in total haemoglobin or red blood cell count between 110 workers at a gas processing plant in Iran (H_2S exposure 0 to 90 ppb [0 to 0.1 mg/m^3; 0 to 0.09 ppm] for 1 to 30 years) and 110 age-matched controls (not exposed to H_2S) (41). However, methaemoglobinaemia was statistically significantly higher in the exposed group than the control group (3.07% [SD 1.16%] versus 0.92% [SD 0.26%], $p<0.001$) and sulfhaemoglobinaemia lower in the exposed group than the control group (0.04% [SD 0.01%] versus 0.05% [SD 0.01%], $p<0.001$), but the clinical relevance of these results is unclear and was not addressed in the study.

Almuhammad and others (study design class D; rated as low quality) reported on changes in liver enzymes in 38 workers at 2 oil and gas facilities in Syria (mean H_2S exposure: 8.6 ppm [12.0 mg/m^3] and 16.3 ppm [22.8 mg/m^3]), compared with 2 control groups (12 nearby residents with a mean exposure to H_2S of 6.1 ppm [8.5 mg/m^3], and 15 non-workers not exposed to H_2S) (39). The levels of 2 enzymes (aspartate aminotransferase – AST, and alanine aminotransferase – ALT) were higher in the exposed workers compared with the unexposed non-worker control group, but there was no evidence of a difference for the other 2 enzymes assessed (gamma glutamyl transferase – GGT, and alkaline phosphatase – ALP). AST was also found to be higher in exposed residents than in unexposed controls. The clinical relevance of these results was not addressed in the study. Additional limitations of this study include incomplete reporting of results, unclear use of summary statistics, and no adjustment for factors that may have impacted the results, although people with chronic or genetic conditions, alcohol dependency and smokers were excluded from the study. Self-reported health symptoms were assessed in 6 participants only, all exposed, and therefore not reported here.

Summary findings – workplace settings (primary studies)

Respiratory outcomes were reported in 2 studies, both cross-sectional studies (study design class D) one rated as medium quality (37) and one rated as low quality (40). One study reported evidence that chronic low-level exposure to H_2S in the workplace may be associated with self-reported respiratory symptoms (40). However, the other cross-sectional study, in which

respiratory outcomes were assessed by an investigator and adjusted for factors such as smoking and BMI, did not find evidence suggesting an association (37).

Neuropsychological motor function was reported in one cross-sectional study (study design class D; rated as medium quality), which identified differences in some of the parameters tested between exposed and unexposed groups, but there was no evidence of a dose-response relationship and the clinical relevance of the results was unclear (36).

Two cross-sectional studies (study design class D; both rated as low quality) reported evidence suggesting an association between chronic low-level occupational exposure to H_2S and some blood markers (methemoglobinemia, sulfhaemoglobinaemia and 2 liver enzymes), but the clinical relevance of these results was not assessed (39, 41).

All 5 studies were cross-sectional (study design class D), with small sample sizes and 3 of the 5 studies rated as low quality (39, 40, 41). Only 2 of the 5 studies provided information about the confounding factors considered in the analyses (36, 37). In addition, 2 of the 5 studies reported on blood markers rather than health outcomes (39, 41), and in one of the remaining 3 studies, health outcomes were self-reported (40). As with studies in community settings, H_2S exposure was assessed by different methods (ambient air monitoring, or by categorising individuals based on typical exposure levels) which may not accurately reflect individual level exposures. Therefore, the overall results of these studies provide weak evidence, both in terms of study design and methodological quality, including lack of adjustment for lifestyle factors and co-exposure to other pollutants.

Table 2. Summary table - primary studies in workplace settings

Reference	Study design	Number of participants	H_2S exposure level (ppm)	Confounders adjusted for	Main findings
Almuhammad and others, 2014 (39) QCC rating: low quality (study design class D)	Cross-sectional	n=65	Mean 8.6 ppm and 16.3 ppm in 2 gas facilities, mean 6.1 ppm in a control group	None reported	Liver enzymes: • increased AST and ALT levels in exposed workers compared to unexposed control group (p≤0.01) • increased AST in exposed residents compared to unexposed control group (p=0.01) • no statistically significant differences reported between groups for GGT or ALP levels
Goffeng and others, 2023 (36) QCC rating: medium quality (study design class D)	Cross-sectional	n=138	H_2S exposure index calculated based on peaks above 0.1 ppm, 1 ppm, 5 ppm and 10 ppm, maximum H_2S level and peak durations	• Age	Neuropsychological motor function tests: • simple reaction time and one of six body sway parameters (intensity) with eyes open statistically significantly higher in the H_2S exposed than the unexposed group (no evidence of dose-response) • no evidence of association for hand co-ordination, other body sway parameters with eyes open, or any body sway parameter with eyes blindfolded • statistically significant association between long-term exposure to H_2S and reduced balance (sway velocity) among smokers
Heldal and others, 2019 (37) QCC rating: medium quality (study design class D)	Cross-sectional	n=148	H_2S exposure index calculated based on peaks above 0.1 ppm, 1 ppm, 5 ppm and 10 ppm, maximum H_2S level and peak durations	Lung function tests adjusted for: • smoking • age • atopy • BMI	• ICAM-1 concentration negatively associated with the H_2S exposure index • No associations identified between H_2S exposure index and lung function tests FEV_1 and FVC
Muzaini and others, 2022 (40) QCC rating: low quality (study design class D)	Cross-sectional	n=191	Mean 1.7 ppm (SD 2.2 ppm)	Unclear if any were included in the analysis	• Individual cumulative H_2S exposure statistically significantly associated with the presence of respiratory self-reported symptoms (adjusted odds ratio 1.04, 95% CI 1.01 to 1.07)
Saeedi and others, 2015 (41) QCC rating: low quality (study design class D)	Cross-sectional	n=220	0 to 0.09 ppm	None reported	• Methaemoglobinaemia 3.07% (SD 1.16%) in the H_2S-exposed group, 0.92% (SD 0.26%) in the control group, p<0.001 • Sulfhaemoglobinaemia 0.04% (SD 0.01%) in the H_2S-exposed group, 0.05% (SD 0.01%) in the control group, p<0.001 • No statistically significant differences between H_2S-exposed and control groups in mean total haemoglobin and red blood cell counts

Acronyms: ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, GGT = gamma glutamyl transferase, H_2S = hydrogen sulphide, ICAM-1 = intercellular adhesion molecule 1, n = number, p = p value, ppm = parts per million, QCC = quality criteria checklist, SD = standard deviation

Limitations

Limitations of the review process

Our rapid review was conducted at pace and followed streamlined methods: for the primary studies, 90% of the records included on title and abstract were screened by only one reviewer, and full text screening and data extraction was done by one reviewer and checked by a second (as per our usual rapid review methods, see Annexe A).

Due to time constraints, it was agreed to limit our searches of primary studies to 2 databases and to use a search filter to exclude animal studies from our results, which could have led to relevant studies being missed. However, we also conducted citation searching (forward, backward and co-citation) in order to increase the chance of retrieving unique relevant studies that may have been missed in our database search.

The main limitation of our methodology was that we used 2 systematic reviews to summarise the evidence published before the PHE toxicological overview (2). As we extracted the review findings as reported within the reviews (no further analysis of the findings was undertaken), our summaries of these reviews are dependent on the quality and reporting of these reviews. The 2 reviews were deemed to be of low and critically low quality based on the AMSTAR 2 assessment. Whilst not ideal, summarising the evidence from the systematic reviews was deemed acceptable by the review team as the main focus of our review was to identify and summarise evidence published since the PHE report (noting that the toxicological overview is a summary of the authoritative body opinions rather than a systematic review of evidence) (2).

The scope of this review was on adverse health outcomes associated with chronic low-level exposure to H_2S; potential beneficial effects were out of scope.

Limitations of the evidence identified

Only 3 of the 15 primary studies identified (published after 2014) were classified as study design class B (prospective cohort studies), therefore providing rather low level of evidence in terms of hierarchy of evidence. Whilst time series, case-crossover, and cross-sectional studies can provide relevant evidence, the conclusions that can be drawn from these studies are limited due to the risk of bias inherent to these study designs (study design classes C and D, see Annexe C).

Of the 15 primary studies, 10 were rated as medium quality, and 5 as low quality. None of the studies were assessed as being of high quality.

The main limitation of the primary studies identified was related to the exposure assessment: across the studies different methods were used to assess H_2S exposure levels, including ambient air monitoring (providing a population-level exposure measurement) and dispersion modelling (an indirect method to estimate average individual exposure at population-level).

There were differences across studies in how the exposure assessment was conducted and reported, including whether meteorological conditions and seasonality were taken into account. Therefore, the exposure levels assigned to individuals, or measured at population-level, may not accurately reflect the level of exposure that individuals experienced.

Another important limitation was the lack of adjustment for lifestyle factors such as smoking, alcohol consumption and physical activity, which may have impacted the results. In addition, the studies were generally conducted in settings where other pollutants (co-exposures) were present. Whilst some studies attempted to take these factors into account, the different pollutant levels were likely to be dependent on each other which may have affected the ability of the researchers to identify the impact of individual pollutants including H_2S.

A further limitation among some of the primary studies identified was related to the selection of participants. This included use of non-representative samples which may have impacted the results of the studies. In addition, some studies lacked clarity on study inclusion criteria or participant characteristics, because of which it is unclear whether the findings can be generalised beyond the participants included in the studies.

These limitations of the primary studies published since 2014 are similar to the limitations identified by the authors of the 2 systematic reviews we used for studies published before 2014, which included use of non-representative samples, assessment of H_2S exposure at population-level, self-reported outcomes, and lack of consideration of other factors which may have impacted the results (such as smoking or other pollutants). Future studies need to address these limitations.

Finally, our ability to draw conclusions from the overall body of evidence was limited due to differences in methodologies (including outcomes measured) and settings between primary studies.

Limitations of the evidence in children

The limitations described in the previous section also apply to the evidence identified in children. In particular, the findings on respiratory outcomes in children should be taken with caution: these results are based on 3 studies at risk of bias due to their study design (one prospective cohort, one time series and one cross-sectional) and the methodological limitations of the studies themselves (including lack of adjustment for factors that may have impacted the results, and potential limitations in how exposure to H_2S was assessed). In addition, the 3 studies were conducted in different settings with different sources of H_2S exposure. Finally, due to the type of outcomes assessed in the prospective cohort and time series studies (hospitalisation), and the design of the third study that assessed lung function (cross-sectional), it was not possible to assess the long-term impact of these outcomes.

It should also be noted that there was no overlap of primary studies reporting on respiratory outcomes in children between the 2 systematic reviews, which limits our confidence that all relevant studies published before 2014 were identified.

To address these limitations, we conducted a rapid review to identify and assess primary studies reporting on the adverse health outcomes of chronic low-level exposure to H_2S in children without restriction on search dates. The methods and results of this rapid review in children (search date: 5 June 2024) are presented in supplementary material 2.

Searching databases from inception (compared to from 2014 as in this current review) did not result in the identification of additional primary studies as only the 3 primary studies mentioned above met the eligibility criteria for our review in children. Therefore, and in line with the findings and limitations described above, results from these 3 studies consistently suggest that chronic low-level H_2S exposure may be associated with some adverse respiratory outcomes in children although this was based on very low certainty evidence which limited our ability to draw conclusions (see supplementary material 2 for further details).

There is a need for higher level evidence (such as prospective cohort studies), which should address the methodological limitations identified (including long-term follow up, and statistical analysis that adjusts for other factors that could impact the results). Demographic and socio-economic data as well as baseline health status should be routinely collected and reported in these studies.

Conclusions

For evidence published prior to the PHE toxicological overview, we summarised 2 systematic reviews identified via an initial scoping search (AMSTAR 2 rating of the reviews: one low quality and one critically low quality; both reviews with a search date in 2014). For evidence published from 2014 onwards, 15 primary studies assessing the adverse health outcomes of chronic low-level H_2S exposure (below 10 ppm, that is, 14.0 mg/m^3) were identified:

- 3 prospective cohort studies (study design class B; QCC rating: medium quality)
- one time series and one time-stratified case-crossover (both study design class C; QCC rating: medium quality)
- 10 cross-sectional studies (study design class D; QCC ratings: medium quality for 5 studies, and low quality for 5 studies)

Due to the limited evidence identified in children, and the lack of overlap between the studies reporting on children identified in the 2 systematic reviews, we conducted an additional rapid review focusing on children (see supplementary material 2), which did not identify additional studies. The conclusions below summarise the overall evidence identified.

H_2S exposure occurred from a range of sources, including natural environmental sources (such as geothermal) and industrial sources (such as petrochemical facilities or sewage treatment plants) in which exposure to other pollutants may have also occurred. The level of H_2S exposure considered in this body of evidence was low, ranging from a mean of 0.000005 ppm to 0.06 ppm in primary studies in community settings, and from 0 to a mean of 8.6 ppm (and 16.3 ppm in one of 2 exposed groups in one primary study) in workplace settings.

Across the systematic reviews and primary studies identified, the outcomes most commonly assessed were respiratory outcomes, followed by neurological outcomes. Other outcomes reported were ocular, cardiovascular, reproductive and developmental, and cancer.

Respiratory outcomes were reported in both systematic reviews and in 9 primary studies published from 2014 onwards (3 prospective cohort, one time series and 5 cross-sectional). Overall, results for respiratory outcomes in adults were mixed (with some studies suggesting evidence of an association, and others reporting no evidence of an association) although the better conducted studies (in terms of assessment of exposure and outcomes, and adjustment for factors such as smoking) did not suggest evidence of adverse long-term respiratory outcomes associated with chronic low-level exposure to H_2S in adults. In children, whilst findings suggested that chronic low-level H_2S exposure may be associated with some adverse respiratory outcomes, this was based on very low certainty evidence which limited our ability to draw conclusions.

Neurological outcomes were reported in both systematic reviews and in 3 primary studies published from 2014 onwards (one prospective cohort, 2 cross-sectional). Overall, results for neurological outcomes in adults were mixed (with some studies suggesting evidence of an association, and others reporting no evidence of an association), although the better conducted

studies (in terms of outcome and exposure assessment) did not suggest an association between chronic low-level exposure to H_2S and adverse neurological outcomes in adults. One study in one systematic review reported neurological outcomes in children, reporting no evidence of an association. To note that this body of evidence was mainly based on cross-sectional studies (therefore providing low-level evidence) and that drawing conclusions from these studies is challenging due to the different outcome measures assessed and lack of adjustment for factors that could have impacted the results (such as co-exposure to other pollutants and lifestyle factors).

Ocular outcomes were reported in one systematic review and in 2 primary studies published from 2014 onwards (one prospective cohort, one cross-sectional). Evidence from the systematic review suggested that chronic low-level exposure to H_2S may be associated with adverse ocular outcomes in adults, although this was based on a limited number of studies, and other factors such as co-exposure to other pollutants and H_2S odour stimulus, may have impacted the results. The 2 primary studies identified since the systematic review was conducted did not report evidence of an association. One study in the systematic review reporting ocular outcomes in children found no evidence of an association.

Cardiovascular outcomes were reported in one systematic review and in 5 primary studies published from 2014 onwards (3 prospective cohort, one time series, one time-stratified case-cross-over) with mixed findings (some studies reporting an association and others reporting no evidence of an association). Whilst the 3 prospective cohort studies included adults and children, results were not reported separately for children. Due to the differences in how the outcomes were assessed, and because of lack of information on, or adjustment for, factors that may have impacted the results (such as smoking, alcohol consumption, or physical activity), our ability to draw conclusions for cardiovascular outcomes is limited.

Cancer outcomes were reported in one systematic review and in 3 primary studies published from 2014 onwards (3 prospective cohort studies, which included both adults and children but results were not reported separately for children). Our ability to draw conclusions was limited due to the limited number of studies identified, the differences in the type of cancer assessed, and the lack of adjustment for individual factors that may have impacted the results.

Reproductive and developmental outcomes were reported in one systematic review, with mixed findings based on limited evidence with methodological limitations. No primary studies reporting on these outcomes were identified through our database search.

Overall, our ability to draw conclusions from the evidence identified was limited by the design of the studies and their methodological limitations, including outcome and H_2S exposure assessment, and the presence of factors that may have impacted the results not accounted for in the analyses (such as individual risk factors and co-exposure to other pollutants). Future research on adverse health effects of chronic, low-level exposure to H_2S should address the methodological limitations identified in this review.

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Disclaimer

UKHSA's rapid reviews aim to provide the best available evidence to decision makers in a timely and accessible way, based on published peer-reviewed scientific papers, unpublished reports and papers on preprint servers. Please note that the reviews: i) use accelerated methods and may not be representative of the whole body of evidence publicly available; ii) have undergone an internal, but not independent, peer review; and iii) are only valid as of the date stated on the review.

In the event that this review is shared externally, please note additionally, to the greatest extent possible under any applicable law, that UKHSA accepts no liability for any claim, loss or damage arising out of, or connected with the use of, this review by the recipient and or any third party including that arising or resulting from any reliance placed on, or any conclusions drawn from, the review.

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Annexe A. Methods

This report followed streamlined systematic methods to address the review question: 'What are the adverse health outcomes of chronic low-level exposure to hydrogen sulphide?'

Our rapid review approach followed streamlined systematic methodologies (7). For instance, full text screening and data extraction were performed by one reviewer and checked by another instead of being conducted in duplicate.

In addition, it was agreed by the review team to use review-level evidence to summarise evidence published before the PHE toxicological overview was conducted (2), and primary studies for more recent evidence. The following protocol applies to the rapid review of primary studies. The method used for the review-level evidence can be found in the main section of the report.

Protocol

A protocol was produced before the literature search began, specifying the review question and the inclusion and exclusion criteria. The protocol is available on request.

Modifications made to the protocol after the review started are reported below, where relevant.

Inclusion and exclusion criteria

Article eligibility criteria are summarised in Table A.1.

Table A.1. Inclusion and exclusion criteria

	Included	Excluded
Population	• Communities living near settings (whether industrial or natural) that emit hydrogen sulphide, although any population or settings meeting the inclusion of low-level chronic exposure will be considered for inclusion	
Exposure	• Chronic low-level exposure to hydrogen sulphide (less than 10 ppm, or 14.0 mg/m^3, [A]	• Acute exposure (less than one year) • High level exposure (greater than 10 ppm)

	Included	Excluded
	on average for one year or more) If duration of exposure is not specified, chronic versus acute will be assessed based on the context of the studies (for example residential exposure likely to be chronic, compared to exposure following an industrial incident which is likely to be acute)	
Outcomes	• Any adverse health outcomes including but not limited to: – neurological – respiratory – cardiovascular – ocular – reproductive – cancer	
Language	English	
Date of publication	1 January 2014 to 2 October 2023 [B]	
Study design	• Cohort studies • Case-control studies • Cross-sectional studies • Ecological studies	• Guidelines • Opinion pieces • Systematic or narrative reviews [C] • Case reports and case series [C] • Animal studies • Experimental studies (such as in vitro studies)
Publication type	• Peer-reviewed	• Conference abstracts • Grey literature

[A] Conversion factor for hydrogen sulphide units from ppm to mg/m^3: 1.40 (6)

[B] From the search dates of 2 relevant systematic reviews identified in the scoping search

[C] Will be coded at the screening stage to be able to draw upon them if needed

Modifications made to the protocol

In relation to outcomes, we identified studies that assessed the impact of H_2S on blood markers. It was agreed with the commissioner to include these studies.

Sources searched

1. Databases used for the literature search: Ovid Medline ALL, Ovid Embase
2. Citation analysis using the included papers, or seed papers (backwards, forwards and co-citation)
3. Additional sources: reference lists of 13 reviews (1, 3-5, 10, 20-27) identified through the scoping and database searches

Search strategies

Databases searches were conducted for papers published between 1 January 2014 and 2 October 2023 (search date: 3 October 2023).

The search strategies were drafted by an information scientist and peer-reviewed by a second information scientist. The search strategies for Ovid Medline ALL and Ovid Embase are presented in Annexe B.

Screening

Results from the database searches were downloaded into Endnote, then duplicates were removed using Deduklick (19) (an automated AI deduplication tool). Final results were imported into Rayyan (16) in order to conduct the screening. Further duplicates were removed in Rayyan before screening started.

Title and abstract screening of records identified was completed in triplicate by 3 reviewers for 10% of the results. Full text screening was done in Rayyan by one reviewer, and checked by a second.

One reviewer screened the reference lists of reviews, and the records identified by the citation searching.

The PRISMA diagram showing the flow of citations is provided in Figure A.1.

Data extraction

Data extraction was conducted by one reviewer and checked by a second. Summary information for each study was extracted and reported in tabular form in a predesigned

template. Information included study settings, study time period, participants, H_2S source and level of exposure, statistical analysis and main findings.

Critical appraisal

Critical appraisal of systematic reviews was conducted using the AMSTAR 2 tool (15). Five questions were considered as critical for this rapid review: Q2 on review methods being established before the review was conducted, Q4 on literature searching, Q9 on validity of the risk of bias assessment, Q11 on meta-analysis, and Q13 on consideration of bias when discussing results. Reviews with one critical flaw were rated as low quality, and those with more than one critical flaw were rated as critically low quality. High quality rating was used for reviews with no or one non-critical weakness only, and the moderate quality rating for reviews having more than one weakness but no critical flaws. Multiple non-critical weaknesses may diminish confidence in the review and in these cases reviewers may downgrade the review rating.

Primary studies were assessed using the QCC for primary research (17, 18). This tool can be applied to most study designs (observational and interventional) and is therefore suitable for rapid reviews of mixed types of evidence. It is composed of 10 validity questions to assess the methodological quality of a study (that is, the extent to which a study has minimised selection, measurement and confounding biases). In the QCC tool, 4 questions are considered critical (on selection bias, group comparability and confounding, and exposure and outcome assessment). A study was rated as high quality if the answers to the 4 critical questions were ‘yes’ (and at least one additional ‘yes’). The study was rated as medium quality if the answer to 50% or more of the critical questions was ‘yes’. The study was rated as low quality if less than 50% of the critical questions were answered ‘yes’ and or if 50% or less of the remaining questions were answered ‘yes’. Judgements were made on case by case for questions answered as ‘unclear’. To note that we report these ratings as ‘quality’ ratings for consistency with the name of the tool, although here quality needs to be understood as ‘methodological quality’ as part of a risk of bias assessment.

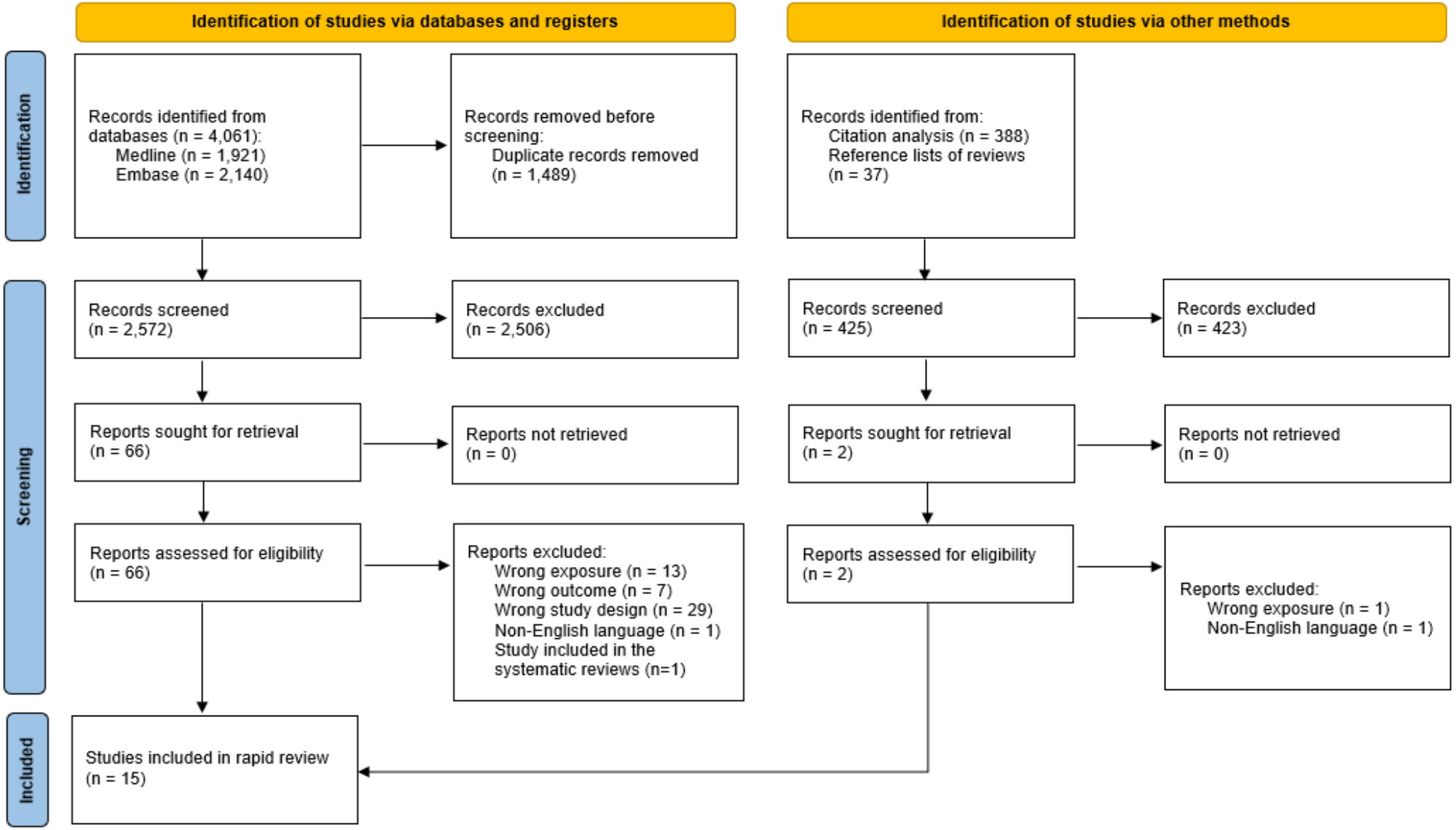
In addition to the QCC rating which provides information about potential for bias within each study design, we took into account the potential for bias inherent to each study design by using a system of study design class, based on the hierarchy of evidence in the Academy of Nutrition and Dietetics Evidence Analysis Manual (18). In this classification, studies in class A have the lowest potential for bias and studies in class D the highest. The overall critical appraisal took into account the study class (or level of evidence) as well as the QCC rating.

Critical appraisal was completed in duplicate by two reviewers. Disagreements were resolved by discussion between the 2 reviewers and further reviewed with the topic advisors. Quality ratings are reported in Table C.1 and Table C.2 (Annexe C).

Synthesis

Narrative synthesis of the evidence identified was performed.

Figure A.1. PRISMA diagram



Text equivalent of PRISMA diagram showing the flow of studies through this review,

From identification of studies via databases and registers, n=4,061 records were identified from databases:

- Medline n=1,921
- Embase n=2,140

From these, 1,489 duplicate records were removed before screening.

After removal of duplicates, n=2,572 records were screened on title and abstract, of which n=2,506 were excluded, leaving n=66 papers sought for retrieval.

The 66 papers were assessed for eligibility on full text (n=0 reports not retrieved). Of these, 51 were excluded:

- wrong exposure n=13
- wrong outcome n=7
- wrong study design n=29
- non-English language n=1
- study included in the systematic reviews n=1

425 additional records were identified through additional sources:

- reference checking from relevant reviews: n=37
- records identified from citation analyses: n=388

Two papers were sought for retrieval and were assessed for eligibility on full text (n=0 reports not retrieved). Of these, 2 were excluded:

- wrong exposure n=1
- non-English language n=1

In total, 15 studies were included.

Annexe B. Search strategy for Ovid MEDLINE and Embase

Search strategy for Ovid Medline ALL (1 January 2014 to 2 October 2023):

1. hydrogen sulfide.tw,kf.
2. hydrogen sulphide.tw,kf.
3. H2S.tw,kf.
4. sour gas.tw,kf.
5. Hydrogen Sulfide/
6. 1 or 2 or 3 or 4 or 5
7. exposure*.tw,kf.
8. long term.tw,kf.
9. chronic.tw,kf.
10. (low* level* or low* limit*).tw,kf.
11. adverse effect*.tw,kf.
12. health effect*.tw,kf.
13. outcome*.tw,kf.
14. communit*.tw,kf.
15. (risk or risks).tw,kf.
16. hazard*.tw,kf.
17. Long Term Adverse Effects/
18. Environmental Exposure/ or Inhalation Exposure/
19. Environmental Pollutants/
20. Epidemiological Monitoring/
21. Hazardous Substances/
22. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 6 and 22
24. exp animals/ not humans.sh.
25. 23 not 24
26. human stud*.tw,kf. or human*.ti.
27. 23 and 26

28. 25 or 27
29. limit 28 to yr="2014 – 2023"

Search strategy for Ovid Embase (1 January 2014 to 2 October 2023):

1. hydrogen sulfide.tw,kf.
2. hydrogen sulphide.tw,kf.
3. H2S.tw,kf.
4. sour gas.tw,kf.
5. Hydrogen Sulfide/
6. 1 or 2 or 3 or 4 or 5
7. exposure*.tw,kf.
8. long term.tw,kf.
9. chronic.tw,kf.
10. (low* level* or low* limit*).tw,kf.
11. adverse effect*.tw,kf.
12. health effect*.tw,kf.
13. outcome*.tw,kf.
14. communit*.tw,kf.
15. (risk or risks).tw,kf.
16. hazard*.tw,kf.
17. community/
18. environmental exposure/ or long term exposure/ or exposure/
19. pollutant/
20. exp epidemiological monitoring/
21. environmental risk/
22. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 6 and 22
24. exp animal/ not human.sh.
25. 23 not 24
26. human stud*.tw,kf. or human*.ti.
27. 23 and 26
28. 25 or 27

29. limit 28 to yr="2014 – 2023"
30. limit 29 to conference abstracts
31. 29 not 30

Annexe C. Critical appraisal

Critical appraisal of systematic reviews

List of AMSTAR 2 questions (15):
Q1. Did the research questions and inclusion criteria for the review include the components of population, intervention, comparator, outcome (PICO)?
Q2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
Q3. Did the review authors explain their selection of the study designs for inclusion in the review?
Q4. Did the review authors use a comprehensive literature search strategy?
Q5. Did the review authors perform study selection in duplicate?
Q6. Did the review authors perform data extraction in duplicate?
Q7. Did the review authors provide a list of excluded studies and justify the exclusions?
Q8. Did the review authors describe the included studies in adequate detail?
Q9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
Q10. Did the review authors report on the sources of funding for the studies included in the review?
Q11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
Q12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
Q13. Did the review authors account for RoB in individual studies when interpreting or discussing the results of the review?
Q14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
Q15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
Q16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

Table C.1 AMSTAR 2 critical appraisal of reviews

Reference	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Overall confidence rating
Lewis and Copley, 2015 (5)	Yes	No	No	Partial yes	Yes	No	No	Yes	Yes	No	NA	NA	Yes	Yes	NA	Yes	Low quality
Lim and others, 2016 (3)	Yes	No	No	No	Yes	No	No	Partial yes	Partial yes	No	NA	NA	Yes	Yes	NA	Yes	Critically low quality

Acronyms: NA = not applicable (typically due to a meta-analysis not being conducted in the review).

Rating system

Five questions were considered as critical for this rapid review (Q2, Q4, Q9, Q11, and Q13). Reviews with one critical flaw were rated as low quality, and those with more than one critical flaw were rated as critically low. High quality rating was used for reviews with no or one non-critical weakness only, and the moderate quality rating for reviews having more than one weakness but no critical flaws. Multiple non-critical weaknesses may diminish confidence in the review and in these cases, reviewers may downgrade the review rating.

Critical appraisal of primary studies

List of Quality Criteria Checklist (QCC) questions (18):

Q1. Was the research question clearly stated?
Q2. Was the selection of study subjects or patients free from bias?
Q3. Were study groups comparable?
Q4. Was the method of handling withdrawals described?
Q5. Was blinding used to prevent introduction of bias?
Q6. Were intervention or therapeutic regimens or exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?
Q7. Were outcomes clearly defined and the measurements valid and reliable?
Q8. Was the statistical analysis appropriate for the study design and type of outcome indicators?
Q9. Are conclusions supported by results with biases and limitations taken into consideration?
Q10. Is bias due to study's funding or sponsorship unlikely?

Study design class

Each study was classified into one of 4 classes based on the hierarchy of evidence (18):

- class A: randomised controlled trials, cluster randomised trials and randomised crossover trials
- class B: prospective cohort studies and retrospective cohort studies
- class C: non-randomised controlled trials, non-randomised crossover trials, case-control studies, time series studies, diagnostic, validity or reliability studies
- class D: non-controlled trials, case studies, case series, other descriptive studies, cross-sectional studies, trend studies, before-after studies

Table C.2. QCC critical appraisal of primary studies

Reference	Study design class	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Overall rating
Almuhammad and others, 2014 (39)	Class D	Yes	No	No	No	Unclear	No	No	Unclear	No	Yes	Low quality
Ancona and others, 2015 (29)	Class B	Yes	Yes	No	Yes	NA	Unclear	Yes	Yes	Yes	Yes	Medium quality
Bates and others, 2015 (34)	Class D	Yes	No	Yes	Unclear	Unclear	No	Yes	Yes	Yes	Yes	Medium quality
Bates and others, 2017 (33)	Class D	Yes	No	Yes	Unclear	Unclear	No	Yes	Yes	Yes	Yes	Medium quality
Finnbjörnsdóttir and others, 2015 (32)	Class C	Yes	Yes	NA	NA	NA	No	Yes	No	Yes	Yes	Medium quality
Finnbjörnsdóttir and others, 2016 (31)	Class C	Yes	Yes	NA	NA	NA	Unclear	Yes	No	Yes	Yes	Medium quality
Goffeng and others, 2023 (36)	Class D	Yes	Yes	No	No	Unclear	Unclear	Yes	Yes	Yes	Yes	Medium quality
Heldal and others, 2019 (37)	Class D	Yes	Yes	No	No	Unclear	Unclear	Yes	Yes	No	Unclear	Medium quality
Hidayati and others, 2020 (38)	Class D	Yes	No	NA	No	No	No	No	No	No	Yes	Low quality
Mataloni and others, 2016 (28)	Class B	Yes	Yes	No	Yes	NA	Unclear	Yes	Yes	Yes	Yes	Medium quality
Muzaini and others, 2022 (40)	Class D	Yes	Yes	NA	No	No	No	No	Unclear	Yes	Yes	Low quality
Nuvolone and others, 2019 (30)	Class B	Yes	Yes	No	No	NA	Unclear	Yes	Yes	Yes	Yes	Medium quality
Pope and others, 2017 (35)	Class D	Yes	No	Yes	Unclear	Unclear	No	Yes	Yes	Yes	Yes	Medium quality
Saeedi and others, 2015 (41)	Class D	Yes	No	No	No	Yes	No	Yes	Yes	No	Yes	Low quality
Yu and others, 2018 (42)	Class D	Yes	Unclear	No	No	Unclear	Unclear	Yes	Yes	No	Yes	Low quality

Acronyms: NA = not applicable.

Rating system

Studies were rated as:

- low quality if the answer to less than 50% of the critical questions was ‘yes’ and or 50% or less of the non-critical questions were answered ‘yes’
- medium quality if the answer to 50% or more of the critical questions was ‘yes’
- high quality if the answer to all of the 4 critical questions (Q2, Q3, Q6 and Q7) was ‘yes’, plus at least one of the non-critical questions

Judgements were made on a case-by-case basis for questions answered as ‘unclear’ to downgrade or upgrade a rating.

About the UK Health Security Agency

UKHSA is responsible for protecting every member of every community from the impact of infectious diseases, chemical, biological, radiological and nuclear incidents and other health threats. We provide intellectual, scientific and operational leadership at national and local level, as well as on the global stage, to make the nation health secure.

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