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Association between odour pollution from industrial sources and human health: a systematic review and meta-analysis

DOCTORAL THESIS

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CERTIFICAMOS

Que la presente Tesis Doctoral titulada **"*Asociación del mal olor procedente de actividades industriales en la salud humana: una revisión sistemática y metaanálisis*"**, que presenta Víctor Guadalupe Fernández para optar al Grado de Doctor por la Universitat de València ha sido realizado bajo nuestra dirección y que se encuentra finalizada y lista para su presentación a fin de que pueda ser juzgada por el tribunal correspondiente.

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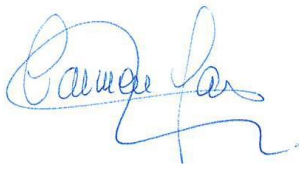

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De acuerdo con la normativa para la *Mención Internacional en el título de Doctor y tesis en régimen de cotutela internacional* (R.D. 99/2011, de 28 de enero, por el que se regulan las enseñanzas oficiales de doctorado) la presente tesis cumple todos los requisitos para la MENCIÓN INTERNACIONAL ("Doctor Internacional"). Entre los requisitos, durante el periodo de formación, Víctor Guadalupe Fernández ha realizado una estancia de investigación en una institución de prestigio internacional por un periodo superior a tres meses.

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VALORACIÓN DE LA ESTANCIA. MENCIÓN INTERNACIONAL

La Comisión Académica del Programa de Doctorado 3139 en Medicina, en su sesión de 21 de mayo de 2019, a la vista de los certificados de realización de la estancia realizada en Departament of Epidemioligy Lazo Regional Health Service, emitidos por los responsables en los Centros de las mismas y de la memoria de la actividad e informe de los Directores/as y en su caso del Tutor/a presentados por D/Dña. VICTOR GUADALUPE FERNÁNDEZ, emite informe favorable sobre la estancia realizada para la obtención de la Mención Internacional en el título de Doctor/a.

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Ref. ***Confirmation of the successful execution of the Short Term Scientific Mission***

This is to certify the successful execution of a Short Term Scientific Mission of Dr. Victor Guadalupe Fernández at the Department of Epidemiology, of the Regional Health Service of Lazio. Dr. Guadalupe Fernández was assigned to work with Senior Environmental Epidemiologist Carla Ancona and Manuela De Sario from the 1st day of November 2018 through the 31st day of January 2019.

Dr. Guadalupe Fernández was involved in a high quality epidemiological research in the field of environmental epidemiology. In particular Victor completed a review of the literature on the effects of the odorigen component of urban waste and conducted a survey on the production of hospital waste in public hospitals related to local health authorities in Rome. Furthermore, he also participated in the campaign to measure road traffic noise levels in Rome.

This experience provided Víctor Guadalupe Fernández with the opportunity to strengthen his research knowledge and experience as part of his doctoral education.

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Marina Davoli

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Preface

"If you cannot measure it, you cannot improve it"

William Thomson

This PhD thesis was written between 2016-2021 at the University of Valencia. It was supervised by Dr. Carmen Saiz and Dean Dr. Antonio Merelles-Tormo. This work comprises a synthesis of the scientific evidence regarding the association between odour pollution and health written by the PhD candidate according to the procedures of the Medicine PhD program of the Department of Preventive Medicine and Public Health, Food Sciences, Toxicology and Forensic Medicine. The initiative was first proposed by the Department of Epidemiology of the Lazio Regional Health Service. During the training period, Víctor Guadalupe Fernández carried out a short-term research stay at the Department of Epidemiology of the Lazio Regional Health Service, Rome, for a period of three months.

The thesis is focused on the association between residential or occupational short and long–term exposure to odour pollution from industrial sources and the health status of the exposed population. This research is presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist. The thesis includes an abstract in Spanish, Valencian, Italian and English, with a general introduction, main objective, methods, results, and conclusions. Data sources includes OvidMedline (1946 to search date), EMBASE (1947 to search date) and Scopus (2004 to search date).

This work was presented as a digital poster in the Final Plenary Conference of the *COST Action Industrially Contaminated Sites and Health Network* (ICSHNet) 2019, in Rome; as an Oral Communication at the XLIII Congress of *Italian Society of Epidemiology – Associazione Italiana di Epidemiologia* (AIE) 2019, in Catania. In addition, the manuscript has been accepted for publication in *Environmental Health*.

Conflicts of interest and funding

The doctoral candidate declares that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Access to data has been made through database consultation and open access.

The author covered research funding for the thesis completion.

List of abbreviations

AFOs: Animal-Feeding Operations
CNS: Central Nervous System
COPD: Chronic Obstructive Pulmonary Disease
CS: Citizen Science
DO: Dynamic Olfactometry
EEA: European Environmental Agency
FI: Field Inspection
FO: Field Olfactometry
GC: Gas Chromatography
I: Intensity
MD: Mean difference
MeSH: Medical Subject Headings
MS: Mass Spectrometry
MSW: Municipal Solid Waste
NTP: National Toxicology Program
ODT: Odour Detection Threshold
OHAT: Office of Health Assessment and Translation
OR: Odds Ratio
ORN: Olfactory Receptor Neuron
OT: Odour Threshold
PECO: Population, Exposure, Comparator, Outcome
PNS: Parasympathetic Nervous System
PR: Prevalence Risk
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL: Quality of Life
REML: Restricted Maximum Likelihood
RoB: Risk of Bias
RR: Relative Risk
RT: Recognition Threshold
SES: Socioeconomic Status
SEs: Surrogate Endpoints
SHC: Subjective Health Complaints
VDI: The Association of German Engineers
VOCs: volatile organic compounds
WHO: World Health Organization
WWTP: Wastewater Treatment Plants

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Resumen/Abstract

Resumen

Introducción

Las emisiones de compuestos olorosos procedentes de actividades industriales constituyen un importante problema de salud para los residentes de barrios cercanos y trabajadores de empresas afectadas, principalmente debido a las molestias olfativas que originan. No obstante, se dispone de poca evidencia sobre el impacto de las molestias olfativas, en comparación con el gran número de estudios que existen sobre la toxicidad de las sustancias químicas emitidas por las actividades industriales, como son el tratamiento de aguas residuales, las explotaciones ganaderas, las instalaciones de compostaje, los vertederos, las fábricas de papel y celulosa o las industrias petroquímicas. Actualmente, la contaminación por olores está regulada por diferentes enfoques en todo el mundo, y es tratada a nivel nacional, regional y local por diferentes marcos legales.

El sentido del olfato juega un papel fundamental en la detección de peligros en el medio ambiente, siendo el tracto respiratorio superior el punto de entrada a través del cual los contaminantes del aire entran en el cuerpo humano. Los receptores olfativos del epitelio nasal pueden detectar compuestos olorosos que inducen sensaciones de diferentes formas. En concentraciones elevadas, los receptores olfativos pueden enviar señales a través del nervio olfatorio y del nervio trigémino hacia el cerebro provocando diferentes reacciones, también conocidas como síntomas subjetivos. Las sensaciones olfativas procesadas en el sistema nervioso central pueden inducir reacciones agradables, cambios en el estado de ánimo hacia emociones positivas, pero también respuestas negativas como pueden ser irritación, dolor, estornudos, salivación y vasodilatación, lo que finalmente puede a su vez resultar en obstrucción nasal, broncoconstricción, secreción de moco e inflamación. Los malos olores, el moho o la mala calidad del aire también se han considerado como desencadenantes ambientales de dolores de cabeza, irritación de los ojos y cansancio inusual. Cabe destacar que las respuestas sensoriales de los individuos pueden variar debido a factores fisiológicos, como son la edad o el sexo, la exposición persistente, el riesgo de salud percibido, además de otros factores sociales. También se ha evidenciado que los síntomas relacionados con el olor podrían ser más comunes en sujetos con

intolerancia a los olores. De hecho, el olor parece no tener un efecto por sí sólo, sino que está mediado por la propia percepción de la persona o la molestia que se origina ante la presencia de un olor. Además, la molestia es un síntoma psicológico que puede estar relacionado con una mala calidad de vida o un estado de ánimo negativo.

Anteriores estudios publicados han evaluado las molestias por compuestos olorosos, y monitoreado el impacto en la comunidad mediante cuestionarios autoinformados sobre las sensaciones que estos les producen, así como sus efectos negativos para la salud, como pueden ser la inflamación y disfunción respiratoria. En este sentido, los cuestionarios estructurados se han aplicado tradicionalmente para recopilar información sobre las características y el estado de salud de la población al abordar la evaluación de los olores.

Las estimaciones de la frecuencia, la intensidad y el tono hedónico del olor en el medio ambiente difieren sustancialmente entre los países, de acuerdo con sus regulaciones o estándares vigentes en relación a sustancias o compuestos olorosos, y no existen métodos estandarizados para la evaluación de olores en la ciencia de la epidemiología ambiental. Además, la percepción de los olores y las respuestas que generan son diferentes entre los individuos, lo que dificulta los esfuerzos para monitorear y evaluar sus efectos sobre la salud. En vista de lo anterior, se considera que las herramientas analíticas de los olores son demasiado poco precisas. Sin embargo, existen algunos enfoques predictivos y de observación que se han utilizado recientemente para estimar la exposición al olor, como son los modelos de dispersión atmosférica, la distancia hasta la fuente originaria del olor, la frecuencia de eventos de olor por año, las pruebas de olfato, el análisis de compuestos químicos y los registros de residentes (respuestas de eventos de olor o porcentaje de residentes molestos por el olor).

Como resultado, el impacto general de las emisiones por compuestos olorosos en la población sigue sin estar claro y ha habido un creciente aumento de la preocupación con respecto a sus posibles efectos en la salud, lo que ha hecho aumentar la cantidad de estudios realizados sobre este tema en las últimas décadas.

Objetivo

Se realizó una revisión sistemática para sintetizar toda la evidencia disponible, de estudios epidemiológicos, sobre la asociación entre la exposición residencial u ocupacional a corto

y largo plazo a la contaminación por mal olor industrial y el estado de salud de la población expuesta.

Métodos

Se registró un protocolo en PROSPERO (número de registro: CRD42018117449).

Criterios de elegibilidad

Los criterios de elegibilidad se definieron en función de la pregunta PECO.

- La población de interés fueron personas de cualquier edad que vivieran cerca de fuentes industriales o trabajadores expuestos a contaminación por mal olor industrial en su lugar de trabajo. La definición de fuente industrial se limitó a todas las instalaciones de producción y plantas de procesamiento de productos químicos, petroquímicos, fabricación, eliminación y / o tratamiento de aguas o desechos, cemento, generación de energía, minería y metales; También se incluyeron otras actividades, como la producción en instalaciones industriales de celulosa y papel, textil, mataderos y explotaciones ganaderas.
- Para la exposición, se incluyeron estudios si capturaban la exposición a un olor ambiental de origen industrial (frecuencia o intensidad del olor auto-informado, concentración de olor…). Se incluyeron estudios si capturaron la exposición a un olor ambiental de fuentes industriales, incluidas medidas objetivas y subjetivas. Se excluyeron los estudios que evaluaron los efectos de la exposición a fuentes de contaminación en interiores. Los estudios que se centraban principalmente en las emisiones de compuestos tóxicos malolientes fueron excluidos, ya que sería difícil discernir entre el efecto del compuesto tóxico con las molestias propias del olor.
- Se incluyeron todos los resultados en salud para los que a priori había una asociación con la exposición (plausibilidad biológica). Se consideraron como resultados en salud primarios, las condiciones clínicas y los síntomas relacionados con el olor, como sibilancias, asma, tos, dolor de cabeza, náuseas/vómitos y molestias por olor; aunque también se incluyeron síntomas relacionados con el estrés y resultados en salud novedosos, como mediciones clínicas y de laboratorio, por ejemplo, hiperreactividad bronquial a la concentración de metacolina o IgE.

Fuentes de información y búsqueda bibliográfica.

Se realizó una búsqueda preliminar en bases de datos bibliográficas para identificar términos de materias y términos libres relevantes para la pregunta de investigación. Posteriormente, se desarrolló una estrategia integral de búsqueda sistemática utilizando una combinación de términos MeSH y términos de texto libre. La estrategia se revisó adecuadamente para cada base de datos para tener en cuenta las diferencias en el vocabulario controlado y las reglas de sintaxis. La búsqueda se implementó del 26 al 27 de octubre de 2018 en Medline (a través de OVID, 1946 hasta la fecha de búsqueda) y EMBASE (1947 hasta la fecha de búsqueda). Para identificar estudios adicionales, se examinó la lista de referencias de los estudios incluidos a través de Scopus (2004 a la fecha de búsqueda). No se establecieron límites sobre la fecha o la ubicación en nuestra estrategia de búsqueda. Se tuvo en cuenta la literatura gris al examinar las bibliotecas de las universidades y los informes nacionales / gubernamentales / de ONG. Además, se estableció contacto con expertos en el tema para obtener información adicional sobre estudios publicados y no publicados.

Selección de estudios

Cargamos los resultados de la búsqueda en un software de gestión de referencias (EndNote, Clarivate Analytics) para gestionar el proceso de selección y codificación. Dos revisores examinaron de forma independiente los títulos y resúmenes de los registros obtenidos de las búsquedas (VFG, MDS). Se recuperó el texto completo de los estudios potencialmente elegibles para su evaluación e inclusión. Cualquier discrepancia con respecto a la inclusión o exclusión de un estudio en particular entre los revisores se resolvió mediante la discusión de un tercer revisor (AC).

Proceso de recopilación de datos y elementos de datos

Para los estudios que cumplieron con los criterios de inclusión, dos revisores extrajeron los datos de forma independiente mediante un formulario de extracción de datos. Los desacuerdos sobre la información extraída se resolvieron mediante discusión con la participación del equipo de investigación cuando fue necesario. Se estableció contacto con tres autores para obtener más información. Todos los autores respondieron, uno de ellos aportó datos numéricos que solo habían sido presentados gráficamente en el artículo

publicado, uno proporcionó un cartel digital, por último, un autor no pudo proporcionar la información solicitada.

De cada estudio, los revisores extrajeron datos sobre el año y el diseño del estudio, el período de muestreo, la región o país donde se realizó el estudio, el tamaño de la muestra (objetivo, sujetos inscritos, tasas de seguimiento) y características de la población, descripción de la referencia grupo control, definición de exposición (fuentes de datos) y evaluación (p. ej., distancia desde la instalación, molestias por olores usando una escala de 5 puntos o modelo de dispersión de compuestos oloroso), resultados de salud recopilados (métodos utilizados para medir el resultado), enfoque estadístico realizado por los autores para analizar los datos, factores de confusión o exposiciones correlacionales (métodos utilizados para medirlos y cómo se consideraron en el análisis), tipo de medida del efecto (índice de riesgo, RR; índice de prevalencia, RP; razón de probabilidades, OR; coeficientes beta; cambio absoluto y relativo) y el intervalo de confianza (IC) del 95%. En el caso de que se dispusiera de más de una medida de efecto del mismo artículo, se aplicaron los siguientes criterios secuenciales pero alternativos (si el primero no aplica, el segundo funciona y así sucesivamente) para elegir la estimación a extraer: el de mejor modelo ajustado; el más significativo; el tamaño de efecto más grande. La información sobre financiación y conflicto de intereses de los autores de los estudios se extrajo y se consideró cuando estuvo disponible.

Evaluación de la calidad de la evidencia

La evaluación de la calidad de la evidencia, así como sus limitaciones metodológicas, se evaluaron mediante una herramienta para medir el riesgo de sesgo entre estudios, especialmente en estudios observacionales, de la *Office of Health Assessment and Translation* (OHAT La revisión sistemática y meta-análisis se diseñó y presento basándose en la declaración PRISMA.

Síntesis de resultados

En relación a los resultados primarios, se agruparon las estimaciones del efecto de cada estudio utilizando modelos de efectos aleatorios (Método *REML* de máxima verosimilitud restringida), siempre y cuando al menos 3 estudios proporcionaran una estimación del

efecto para ese resultado en salud comparando sujetos expuestos versus no expuestos. La heterogeneidad entre estudios se evaluó utilizando el estadístico de *Higgins* I^2.

Resultados

Nuestra búsqueda identificó 5728 registros después de la eliminación de duplicados. De estos, se descartaron 5654 en base al título y resumen. No se identificó ningún estudio a partir de fuentes de literatura gris. Posteriormente, se incluyeron 74 registros en la evaluación de texto completo. De ellos, se incluyó un total de 29 estudios en la síntesis final, incluidos dos registros adicionales identificados a través de la búsqueda inversa en lista de referencia de los estudios incluidos.

Características de los estudios

Del total de estudios incluidos en la revisión, 23 fueron estudios transversales. Se incluyeron poblaciones mixtas de hombres y mujeres adultos, un estudio con una muestra en edad escolar y dos estudios con trabajadores expuestos como población de interés. La ganadería intensiva, así como la gestión de residuos, fueron las actividades industriales más destacadas por la evidencia como principales fuentes de exposición a olores ambientales.

La información sobre la exposición y los resultados en salud se obtuvo principalmente mediante cuestionarios auto-reportados basados en escalas *Likert* y otras escalas alternativas. Sólo cuatro estudios utilizaron mediciones clínicas y de laboratorio como resultados en salud primarios. Se extrajeron un total de 98 resultados en salud de los estudios. Muchos estudios a menudo no proporcionaban una estimación del tamaño del efecto entre la exposición y el resultado en salud descrito, por tanto, en estos casos, sólo fue posible su presentación de forma descriptiva. Se encontraron cuarenta y siete resultados en salud reportados una única vez entre los estudios incluidos. Los resultados más comúnmente estudiados fueron el dolor de cabeza y las náuseas/ vómitos.

Riesgo de sesgo de los estudios incluidos

En general, el conjunto de la evidencia se vio afectado por un riesgo de sesgo definitivamente alto en la determinación de la exposición y de los resultados, ya que la mayoría de los estudios utilizaron información auto-reportada. Se clasificaron 16 estudios

en el peor nivel de calidad (3er nivel), 9 estudios en el segundo (2º nivel) y 5 estudios en la primera categoría (1er nivel).

La confianza en la determinación de la exposición y los resultados en salud fue muy baja en la mayoría de los estudios. Solo tres estudios se consideraron de bajo riesgo de sesgo, ya que utilizaron medidas de estimación de la exposición y de los resultados en salud objetivas. Otro problema crítico fue la falta de control de otras exposiciones (por ejemplo, contaminación del aire).

En cuanto a los factores de confusión, se logró un ajuste mínimo de posibles factores de confusión en la mayoría de los estudios para los que el riesgo de sesgo se etiquetó como bajo. Sin embargo, once estudios, que no tuvieron en cuenta ningún factor de confusión, se clasificaron como riesgo de sesgo "probablemente alto" o "definitivamente alto". El segundo elemento de confusión se refirió al ajuste de otra exposición ambiental y, en este caso, la mayoría de los estudios no se ajustaron por exposiciones concurrentes. El tercer elemento de confusión con respecto a la validez y confiabilidad de las medidas se caracterizó por un alto riesgo de sesgo en la mayoría de los estudios, ya que la información fue principalmente auto-reportada, como datos basados en cuestionarios.

El riesgo de sesgo de selección resultó ser alto en cinco estudios, ya que el grupo de control no pudo considerarse no expuesto. No se proporcionó información sobre si la selección de los participantes del estudio resultó en grupos de comparación apropiados en ocho estudios. Sólo tres estudios se clasificaron en "riesgo definitivamente bajo" de sesgo de deserción. Se consideró que cinco estudios tenían un alto riesgo de sesgo de informe y, además, dos estudios, tenían un riesgo poco claro ya que los resultados no se informaron con suficiente detalle, muy probablemente porque representaban comunicaciones breves. Un riesgo probablemente bajo de sesgo de notificación se encontró en un estudio, después de evaluar una publicación previa de otra parte de los resultados.

Con respecto al uso de métodos estadísticos apropiados, once estudios se consideraron de alto riesgo (probable o definitivamente) ya que solo proporcionaron un análisis descriptivo.

<u>Efectos sobre la salud del olor industrial</u>

Los resultados en salud se agruparon de la siguiente manera: malestar general (p. Ej., dolor de cabeza, problemas para dormir), síntomas gastrointestinales (p. Ej., náuseas / vómitos, reflujo), síntomas de las vías respiratorias inferiores y superiores (p. Ej., tos / flema, sibilancias), función inmunitaria / alergia, irritación de la mucosidad, trastornos de la piel, estado de ánimo, problemas cardiovasculares y molestias por olores (p. Ej., molestias por olores, percepción de riesgo). Se realizó meta-análisis para dolor de cabeza, náuseas / vómitos y tos / flema. Los apéndices también informaron los resultados no incluidos en los meta-análisis. No se dispuso de medida de asociación en cinco estudios.

Síntomas generales de enfermedad

Diecinueve estudios analizaron los síntomas de enfermedades generales como resultado de los efectos relacionados con el olor en la salud. Todos los estudios se realizaron en adultos. Se realizaron dos estudios en trabajadores.

El dolor de cabeza fue el síntoma de enfermedad general más común, y se informó en dieciséis estudios. El análisis agrupado mostró un aumento del riesgo de dolor de cabeza en los expuestos frente a los no expuestos (OR = 1,15, IC del 95%: 1,01 a 1,29) con heterogeneidad moderada (I^2 = 66%, valor de p = 0,004).

Entre los estudios no incluidos en el meta-análisis, diez estudios evaluaron la exposición al olor de manera objetiva, informando escasa evidencia de asociación con mareos, dificultades para dormir, fatiga, dolor en las articulaciones, fiebre durante los últimos 12 meses y dolor de muelas.

Entre los estudios que evaluaron la exposición subjetivamente, se encontraron asociaciones más consistentes para mareos, fatiga no natural y dolor articular / muscular. Entre los trabajadores expuestos, se encontró una elevación significativa del total de la puntuación de molestias subjetivas de salud (SHC) y la puntuación de molestias subjetivas neurológicas en los trabajadores expuestos.

Síntomas gastrointestinales

Quince estudios informaron síntomas gastrointestinales. Todos los estudios se realizaron en adultos. Solo un estudio incluyó trabajadores.

El síntoma gástrico más frecuentemente informado fue náuseas y vómitos. Siete estudios fueron factibles para el meta-análisis y mostraron un mayor riesgo de estos síntomas (OR = 1,09; IC del 95%: 0,88 a 1,30) con una heterogeneidad baja (I^2 = 28,3%; valor de p = 0,193).

Entre otros síntomas gástricos, ocho estudios midieron la exposición de manera objetiva. La alta exposición a los olores se asoció con una mayor prevalencia de pérdida de apetito (OR = 4,27; IC del 95%: 1,43 a 12,73). Un estudio mostró una mayor frecuencia de síntomas gástricos (disgusto, pérdida de apetito, malestar estomacal) al aumentar la frecuencia de exposición al olor. Otro estudio informó una tendencia significativa por área entre las mujeres que habían informado de estreñimiento frecuente u ocasional.

Siete estudios evaluaron la exposición subjetivamente. Un estudio mostró que la diarrea era más frecuente en personas con intolerancia al olor (OR = 2,18, IC del 95%: 1,43 a 3,33) o que experimentaban problemas de salud relacionados con el mal olor (OR = 2,83, IC del 95%: 1,82 a 4,4); sin embargo, el mismo estudio no informó ninguna asociación significativa en personas con quejas no relacionadas con la salud (OR = 1,08, IC del 95%: 0,74 a 1,58). Se encontró un mayor riesgo de diarrea en el grupo con percepción de olores (OR = 1,3, IC del 95%: 1 a 1,7) y con molestias por olores (OR = 1,2, IC del 95%: 0,9 a 1,7). También se informaron asociaciones estadísticamente significativas con dolor de estómago, síntomas gastrointestinales y estreñimiento. No se observaron diferencias en la puntuación gastrointestinal entre los grupos de trabajadores.

<u>Síntomas de las vías respiratorias inferiores</u>

Quince estudios informaron sobre la asociación entre los síntomas de las vías respiratorias inferiores y la contaminación por olores. Todos los estudios se realizaron en adultos excepto uno. No se realizó ningún estudio sobre los trabajadores.

Once estudios informaron que la tos y la flema eran síntomas que se relacionaban con el olor. El análisis agrupado mostró un efecto de 1,27 (IC del 95%: 1,10 a 1,44), con heterogeneidad moderada (I^2 = 53,8%, valor de p = 0,043).

Entre otros síntomas respiratorios, nueve estudios informaron la exposición de manera objetiva, utilizando la distancia como indicador principal de la exposición. Sólo tres

estudios informaron hallazgos significativos sobre sibilancias, asma y dificultad para respirar.

Entre los estudios que evaluaron la exposición subjetivamente, ocho informaron efectos significativos en la salud. Se evidenciaron estimaciones más consistentes para el asma, mientras que las asociaciones con sibilancias fueron más débiles. Un estudio mostró que el olor de las instalaciones ganaderas se relacionó significativamente con la dificultad para respirar (PR = 1,52, IC del 95%: 1,02 a 2,27) y aumentó la presencia de enfermedades respiratorias inferiores (diferencia media = 0,28, IC del 95%: 0,05 a 0,5) para el grupo de olor moderado / fuerte / muy fuerte. Además, las personas que se quejaban de intolerancia a los olores tenían una mayor prevalencia de infecciones respiratorias auto-reportadas (OR = 4,81, IC del 95%: 3,24 a 7,14) o EPOC (OR = 2,95, IC del 95%: 1,84 a 4,73), y se encontraron hallazgos similares para el grupo de personas con molestias con impacto en la salud versus sin molestias por EPOC (OR = 2,05; IC del 95%: 1,21 a 3,49). También existe un mayor riesgo de tos duradera y EPOC en personas con molestias olfativas en términos de una amenaza para la salud, sin embargo, la precisión de la estimación del efecto es menor en este sentido. No se encontró asociación entre el olor y el dolor torácico en los estudios incluidos.

Sólo dos estudios evaluaron la función pulmonar y la hiperreactividad bronquial. En ambos estudios se encontró una reducción en el PEF y el FEV_1 con el aumento del olor; sin embargo, los IC del 95% incluyeron el valor nulo. Además, no se observaron asociaciones entre la molestia por olor autor-reportada y la hiperreactividad bronquial a la metacolina.

Alergias y síntomas de las vías respiratorias superiores

Diez estudios presentaron datos sobre asociaciones entre olores y síntomas de las vías respiratorias superiores. Todos los estudios se realizaron en adultos. Solo se realizó un estudio en trabajadores.

En relación con los estudios con exposición objetiva, no se encontraron asociaciones consistentes entre la distancia y la frecuencia de resfriado / gripe, secreción nasal, congestión nasal y rinitis no alérgica. En cuanto a los estudios con exposición subjetiva, solo en tres estudios se evidenció un mayor riesgo de secreción nasal asociado a mayor

incremento del olor percibido. Se encontró una asociación límite entre el resfriado / gripe en el último mes y la molestia por olores (OR = 1,38, IC del 95%: 0,97 a 1,99). En el único estudio realizado en trabajadores, no hubo diferencias significativas entre la puntuación de la gripe en los sujetos expuestos y el grupo de control.

Cinco estudios evaluaron el efecto del olor en el sistema inmunológico y la sensibilización alérgica mediante la estimación de la concentración de IgE e IgA y una puntuación de alergia, pero no se evidenció un incremento significativo de estos resultados conforme la exposición al olor aumentó.

Irritación de las mucosas y trastornos de la piel.

Doce estudios evaluaron el efecto del olor sobre la irritación de las mucosas, y seis estudios evaluaron su efecto sobre la piel. Todos los estudios se realizaron en adultos. No se realizó ningún estudio en trabajadores.

Seis estudios evaluaron la aparición de síntomas de irritación objetivamente a través de la distancia con respecto a la fuente industrial, encontrándose efectos significativos relacionados con la prevalencia de sequedad de garganta durante los últimos 12 meses, irritación de la nariz e irritación de la piel. Con respecto a los estudios con exposición subjetiva del olor, se encontraron hallazgos significativos para la irritación ocular / ardor ocular y dolor de garganta / sequedad de garganta / ardor de garganta en cinco estudios (tolerancia y percepción del olor), para la irritación de la nariz / ardor nasal en dos estudios, para la nariz / síntomas de irritación ocular en un estudio y para la irritación / erupción cutánea en tres estudios.

Estado de ánimo

Trece estudios consideraron que el mal olor puede tener un impacto en el estado de ánimo. Todos los estudios se realizaron en adultos. Un estudio se centró en los trabajadores.

Seis estudios evaluaron la exposición de manera objetiva. Solo se informaron asociaciones significativas de nerviosismo y dificultad para concentrarse.

Nueve estudios evaluaron la exposición subjetivamente. Se encontraron asociaciones significativas para todos los resultados evaluando el estado de ánimo en un estudio, para

el nerviosismo, la ira, el estrés, la infelicidad también se encontraron en otro estudio, y para la tristeza y los síntomas relacionados con el estrés en un tercer estudio. También se encontró una asociación dosis-respuesta entre la molestia por olores y la dificultad para concentrarse. Además, los trabajadores en el grupo de puntuación de olor alta informaron una puntuación postraumática más alta.

Signos y síntomas del sistema cardiovascular

Tres estudios evaluaron los efectos del olor sobre los síntomas cardiovasculares y la presión arterial. Cada unidad de aumento de olor en una escala de 8 puntos se asoció con aumentos en la presión arterial diastólica (mmHg) (OR = 1,26; IC del 95%: 1,08 a 1,47) pero no en la presión arterial sistólica. No se encontró asociación significativa en los otros dos estudios.

Molestias por olores

Diez artículos investigaron las molestias de los olores en la población con respecto a su proximidad a las industrias, la percepción de olores, la frecuencia o intensidad de los olores, el tono hedónico y la exposición al amoniaco (NH_3). Todos los estudios se realizaron en adultos. No se realizó ningún estudio en trabajadores.

En relación con los estudios que evalúan la exposición objetivamente, se encontró una asociación significativa entre la molestia por olores y la frecuencia de los olores, la concentración de NH_3 y la exposición a los olores a través de modelización (dispersión). Además, en otros tres estudios también se encontró un aumento significativo en las molestias por olores en las áreas más cercanas a la fuente olorosa. En cuanto a los estudios que evalúan la exposición subjetivamente, en un estudio se encontró una asociación dosis-respuesta significativa con molestias por olores, consistente en las diferentes medidas de exposición (frecuencia, intensidad, tono hedónico del olor), agravando el efecto en sujetos severamente molestos. En otro estudio, la última asociación fue consistente entre las fuentes olorosas (viviendas para ganado, purines y estiércol, ganadería en general).

Conclusiones

En esta revisión sistemática y meta-análisis, resumimos el conocimiento actual sobre los efectos en la salud de la exposición a la contaminación por olores procedentes de

actividades industriales. Se han examinado distintos resultados, que han usado diferentes criterios de evaluación, para medir su efecto y evaluar su plausibilidad biológica en la población objeto de estudio.

Este estudio proporciona un apoyo considerable a las conclusiones científicas adoptadas en el proyecto *The Distributed Network for Odour Sensing, Empowerment and Sustainability* (D-NOSES) y sugiere efectos en salud adicionales que se asocian con la contaminación por olores. Entre los principales hallazgos hasta la fecha se encuentran los siguientes:

1. Se han estudiado tanto la exposición residencial como ocupacional, sin embargo, solo dos estudios incluyeron una evaluación de la exposición ocupacional en su diseño de estudio, por lo que no se pudieron sacar conclusiones al respecto. En relación con los efectos de la exposición a olores en el ámbito residencial, a pesar de que se han publicado e incluido una amplia variedad de estimaciones de los efectos de la contaminación por olores en este estudio, la evidencia aún es limitada sobre sus efectos potenciales en el estado de salud de la población expuesta.
2. Solo 29 estudios cumplieron los criterios de calidad metodológica mínima necesarios para su inclusión después de una evaluación minuciosa. Solo se incluyeron 9 manuscritos en la síntesis cuantitativa (meta-análisis).
3. Se informaron 98 resultados al menos una vez. Se ha observado una elevada prevalencia de síntomas relacionados con el olor, como dolor de cabeza, tos / flema, náuseas / vómitos, sibilancias y asma, entre la población expuesta a las actividades industriales de los estudios incluidos. Dada la carencia de mediciones objetivas de la exposición y de los resultados en los estudios incluidos, la comparación de los efectos estimados fue limitada y los resultados se presentaron principalmente de forma descriptiva.
4. El meta-análisis solo fue factible de realizarse para 3 resultados en salud, y se observó una asociación significativa entre la exposición a olores residenciales y el dolor de cabeza, la tos / la flema, y débilmente asociado a las náuseas / los vómitos, que fue de significación estadística marginal.
5. Para otros resultados como asma / sibilancias, estados de ánimo y síntomas de irritación de la mucosidad, entre otros, existen motivos razonables para creer que una exposición mayor y prolongada a la contaminación por olores puede estar

asociada con una mayor prevalencia de síntomas relacionados con el asma, signos relacionados con el estado de ánimo e irritación de la mucosidad. En este punto, cabe señalar que el número de estudios no permitió una síntesis cuantitativa de estos resultados.

6. En cuanto a la calidad de los estudios incluidos, las posibles fuentes de errores de medición, debido a que los resultados de salud se basaron únicamente en información auto-reportada, limitaron nuestras conclusiones sobre los patrones de dosis-respuesta. De acuerdo con anteriores revisiones críticas sobre este tema, nuestros hallazgos identificaron un mecanismo evidente relevante para la plausibilidad biológica de la asociación entre la exposición a la contaminación por olores de actividades industriales y el estado de salud de la población.
7. Esta revisión llena un vacío de investigación porque sólo otra revisión publicada ha utilizado un enfoque sistemático en este campo de estudio. El enfoque de revisión sistemática permitió realizar una síntesis de literatura científica válida, fiable y reproducible con el apoyo de personas con experiencia como Coordinadores de Búsqueda de Ensayos Cochrane. Además, se utilizaron diferentes bases de datos bibliográficas para encontrar diferentes efectos sobre la salud relacionados con los olores en la población general y para evaluar la variabilidad de los estudios que evalúan el impacto de los olores de las distintas fuentes industriales. Además, se aplicó la herramienta OHAT para evaluar la calidad de los estudios incluidos y la calidad de la evidencia en general. No se dispone de un estándar de oro para evaluar la calidad de los estudios observacionales, especialmente en salud ambiental. Sin embargo, esta revisión muestra que la herramienta OHAT podría ser útil para esta tarea.
8. La evidencia general es de calidad "baja" - "muy baja", lo que respalda la necesidad de estudios de mayor calidad, especialmente en relación con el diseño del estudio (p. Ej., estudios de panel), la evaluación de la exposición (p. Ej., Modelos de dispersión) y la evaluación de resultados. (por ejemplo, medidas objetivas). En particular, el efecto del olor debe ajustarse a la percepción o molestia individual; de lo contrario, la asociación podría estar sesgada. La mayoría de los estudios señalaron que la molestia y los síntomas asociados al olor podrían estar mediados por el olor percibido y la percepción de riesgo para la salud, además de otros factores relativos a la propia persona.

Abstract

Introduction

Odour emissions from industrial sites constitute a major health issue for neighbouring residents and workers, mainly due to the olfactive nuisances that they engender. Nevertheless, little evidence is available on the impact of olfactory nuisance, compared to a large number of studies on the toxicity of the chemical substances emitted by industrial activities such as wastewater treatment, livestock operations, composting facilities, landfills, paper and pulp mills or petrochemical industries. Odour pollution is regulated by different approaches worldwide, and it is addressed at a national or municipal level by different policy frameworks.

The olfactory function plays an important role in the detection of hazards in the environment, with the upper respiratory tract usually being the first point through which air pollutants enter the human body. Olfactory receptors of the nasal epithelium may detect odorant compounds inducing sensations in different ways. At elevated concentrations, odorant receptors may send signals via the olfactory and trigeminal nerve to the brain causing different reactions, also known as subjective symptoms. Odour sensations processed in the central nervous system may induce pleasant reactions, positive moods and emotions, but also negative responses, including irritation, pain, sneezing, salivation, and vasodilation, ultimately resulting in nasal obstruction, bronchoconstriction, mucus secretion and inflammation. Malodours, mould or bad air quality have also been considered as environmental triggers of headaches, eyes irritation, and unusual tiredness. It is also important to note that individuals' sensory responses may vary due to physiological factors, age or sex, persistent exposure, perceived health risk, and various social factors. Odour-related symptoms seem more common in subjects with odour intolerance. In fact, odour seems to not have an effect *per se*, but it is mediated by personal perception or annoyance. Furthermore, annoyance is a psychological symptom that can be related to poor quality of life or negative mood states.

Several studies measure odour annoyance and monitor community impact by self-reporting of somatic symptoms, as well as objective health effects, commonly including respiratory inflammation and dysfunctions diagnosed by physicians. The population's

characteristics and health status have traditionally been considered in surveys and structured interviews when approaching odour assessment.

Estimations of odour frequency, intensity and hedonic tone in the environment differ substantially among countries, according to their odour regulations, and there are no standardized methods for odour assessment in environmental epidemiology. Besides, people's sensitivity and odour responses are different among individuals, hindering efforts to monitor and assess its health effects. In view of the above, it is considered that odour analytical tools are not sufficiently accurate. However, there are some predictive and observational approaches that have been used to estimate odour exposure, such as atmospheric dispersion models, distance to the source, frequency of odour events per year, sniff tests, chemical compounds analysis, recordings from residents (odour responses or percent of highly annoyed residents).

As a result, the overall impact on communities by odour emissions remains unclear and there has been a rising number of concerns and complaints regarding their possible health effects, ending up increasing the quantity of studies performed on this topic lately.

Objective

A systematic review was conducted to synthesize all the available evidence from epidemiological studies about the association between residential or occupational short and long–term exposure to odour pollution from industrial sources, and the health status of the exposed population.

Methods

A protocol was registered at PROSPERO (registration number: CRD42018117449).

Eligibility criteria

Eligibility criteria were defined based on the PECO statement.

- The population of interest were people of any age living near industrial sources or workers exposed to odour pollution in their workplace. The definition of an industrial source was limited to all production facilities and processing plants for chemicals, petrochemicals, manufacturing, waste or water disposal and/or

treatment, cement, power generation, mining and metals; other activities were also included, such as production in industrial installations of pulp and paper, textile, slaughterhouses and livestock operations.

- Studies that captured and measure any environmental odour from industrial activities, assessed by subjective and/or objective measurements, were included. Nevertheless, studies that were mainly focused on emissions of malodorous toxic compounds were excluded due to their difficulties to disentangle the odour effect from the chemical one. Furthermore, studies that assessed the effects of exposure of indoor odour pollution were also excluded.
- We included all health outcomes for which there was *a priori* association with the exposure (biological plausibility). We considered clinical conditions and odour-related symptoms, such as wheezing, asthma, cough, headache, nausea/vomiting and odour annoyance, as primary reported outcomes,; although we also included stress-related symptoms and novel outcomes, like laboratory and clinical measurements, for example, the bronchial hyperresponsiveness to methacholine or IgE concentration.

Information sources and search

A preliminary search was conducted in bibliographic databases to identify subject terms and free terms relevant to the review question. Afterwards, a comprehensive systematic search strategy was developed using a combination of MeSH terms and free text terms. The strategy was revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules. The search was implemented on October 26-27, 2018, in Medline (via OVID, 1946 to search date) and EMBASE (1947 to search date). To identify additional studies, the references list of included studies was screened through Scopus (2004 to search date). No limits about date or location were set in our search strategy. Grey literature was taken in consideration by examining different university libraries, and national/government/NGO reports. Furthermore, experts on the topic were contacted for additional information about unpublished and published studies.

Study selection

Search results were uploaded into a reference management software to manage the screening and coding process. Two reviewers independently screened titles and abstracts

of the records obtained from the searches (VFG, MDS). The full texts of potentially eligible studies were retrieved for evaluation and inclusion. Any discrepancies regarding inclusion or exclusion of a particular study between reviewers were resolved through discussion by a third reviewer (CA).

Data collection process and data items

For studies that met inclusion criteria, two review authors independently extracted data using a data extraction form. Disagreements about the extracted information were resolved by discussion with the involvement of the research team when necessary. Three authors were contacted for further information. All authors responded, one of them provided numerical data that had only been presented graphically in the published article, one provided a digital poster while the one remaining author could not provide the requested information.

Furthermore, the reviewers extracted data on study year and design from each study, sampling time frame, region or country where the study was performed, sample size (target, enrolled, follow-up rates) and characteristics of the population, description of the reference or control group, exposure definition (data sources) and assessment (e.g., distance from the facility, odour annoyance using a 5-point-likert scale, dispersion modelling), health outcomes assessed (methods used to measure the outcome), missing data, statistical approach performed by the authors to analyse the data, confounders or co-exposures (methods used to measure them and how they were considered in analysis), type of effect measure (Risk Ratio, RR; Prevalence Ratio, PR; Odds Ratio, OR; beta coefficients; absolute and relative change) and the 95% confidence interval (CI). Information on funding and conflict of interest by the authors of the studies was extracted and considered when available.

Risk of bias assessment in individual studies

The confidence in the entire body of evidence and methodological limitations were assessed using the Office of Health Assessment and Translation (OHAT) Risk of Bias tool. The results were structured and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Data synthesis

For primary outcomes, in cases in which at least 3 studies provided effect estimates by comparing exposed subjects versus not exposed, we pooled the study-specific estimates of odour-related effect using random effects models (Restricted Maximum Likelihood REML Method). Heterogeneity was evaluated with Higgins I^2.

Results

5728 records were identified after the removal of duplicates. Of these, 5654 were discarded on the base of title and abstracts. No study was identified from grey literature sources. 74 records were subsequently included in the full-text evaluation. From those, a total of 29 studies were included in the final synthesis including two additional records identified through reference list of the studies.

Study characteristics

Of the total number of the studies eligible for this review, 23 were mainly cross-sectional design. Mixed populations of adult males and females were included, with only one study involving a sample of school-age children and two studies involving workers. Animal Feeding Operations and waste were the most common industrial sources.

Exposure and outcome information was most commonly obtained by self-report based on Likert scales. Only four studies reported laboratory and clinical measurements as primary outcomes. A total of 98 outcomes were extracted from the studies. Reported outcomes did not necessarily provide effect size in all studies, however, some authors occasionally only presented results descriptively. 47 outcomes were reported only once. The most commonly studied outcomes were headache and nausea/vomiting.

Risk of bias in the included studies.

Overall, the body of evidence was affected by a "definitely high" risk of bias in exposure and outcome assessment, since most studies used self-reported information. 16 studies were classified in the worst quality level (3rd tier), 9 studies in the second (2nd tier) and 5 studies in the first category (1st tier).

Confidence in exposure and outcome assessment was very low in most studies. Only three studies were judged at low risk of bias since they used objective outcomes or exposure

measures. Another critical issue was the lack of control for other co-exposures (e.g., air pollution).

As for confounding, the adjustment with a minimum set of potential confounders was achieved in most studies for which the risk of bias was labelled low. However, eleven studies that did not account for any confounders, were graded at "probably high" or "definitely high" risk of bias. The second confounding element referred to the adjustment of other environmental exposure, and in this case, most studies did not adjust for concurrent exposures. The third confounding element regarding validity and reliability of measures was characterized by a high risk of bias in most studies, since information was mostly self-reported.

The risk of selection bias resulted to be high in five studies since the control group could not be considered unexposed. In eight studies, no information was provided as to whether the selection of study participants resulted in appropriate comparison groups. Only three studies were classified at "definitely low risk" of attrition bias. Five studies were judged at high risk of reporting bias and, additionally, two studies were at unclear risk since outcomes were not reported with sufficient detail in the short communications. A "probably low" risk of reporting bias was found in one study, after evaluating a previous publication of another part of the results.

Regarding the additional element of appropriate statistical methods, eleven studies were judged at high risk (probably or definitely) since they provided only a descriptive analysis.

Health effects of industrial odour

Health outcomes were grouped as follows: general ill feelings (e.g. headache, sleeping problems), gastrointestinal symptoms (e.g. nausea/vomiting, reflux), lower and upper respiratory symptoms (e.g. cough/phlegm, wheezing), immune function/allergy mucus irritation, skin disorders, mood states, cardiovascular problems, and odour nuisances (e.g. odour annoyance, risk perception). We ran meta-analyses for headache, nausea/vomiting and cough/phlegm. Appendices also reported the results that were not included in the meta-analyses. No measure of association was available for five studies.

General ill symptoms

Nineteen studies analysed general ill symptoms as health outcome of odour related effects. All studies were on adults. Two studies were conducted among workers.

Headache was the most common general ill symptom, being reported in sixteen studies. Pooled analysis showed an increased risk of headache in exposed versus not exposed (OR=1.15, 95% CI: 1.01 to 1.29) with moderate heterogeneity (I^2 = 66%, p-value = 0.004). Among studies that were not included in the meta-analysis, ten studies evaluated exposure to odour objectively, reporting sparse evidence of association for dizziness, sleeping difficulties, fatigue, joint pain, fever past 12 months, and toothache. Among studies evaluating exposure subjectively, most consistent associations were found for dizziness, unnatural fatigue and joint/muscular pain. Among exposed workers, significant higher total subjective health complaint (SHC) score and the subjective neurological complaints score were found in exposed workers.

Gastrointestinal symptoms

Fifteen studies reported gastrointestinal symptoms. All studies were on adults. Only one study included workers.

The most frequent gastric symptom reported was nausea/vomiting. Seven studies were feasible to meta-analysis, showing an increased risk of these symptoms (OR=1.09; 95% CI: 0.88 to 1.30) with a low heterogeneity (I^2 = 28.3%; p-value=0.193). Among other gastric symptoms, eight studies measured exposure objectively. High exposure to odours was associated with greater prevalence of loss of appetite (OR = 4.27; 95% CI: 1.43 to 12.73). One study showed a higher frequency of gastric symptoms (disgust, loss of appetite, stomach discomfort) when the frequency of odour exposure was increased. Another study reported a significant trend by area among women who had reported frequent or occasional constipation. Seven studies evaluated exposure subjectively. One study reported more frequent diarrhoea in people with self-reported odour intolerance (OR = 2.18, 95% CI: 1.43 to 3.33) or experiencing malodour-related health complaints (OR = 2.83, 95% CI: 1.82 to 4.4); however, the same study did not report any significant association in people with complaints that were not related to health (OR = 1.08, 95% CI: 0.74 to 1.58). An increased risk of diarrhoea was found in the groups with odour perception (OR = 1.3, 95% CI: 1 to 1.7) and with odour annoyance (OR = 1.2, 95% CI: 0.9 to 1.7). Statistically significant associations with stomach pain, gastrointestinal

symptoms and constipation were also reported. There were no observed differences between groups for the gastrointestinal score among workers.

Lower respiratory symptoms

Fifteen studies reported the association of lower respiratory symptoms with odour pollution. All studies were on adults except one. No study was conducted on workers.

Eleven studies reported cough and phlegm as odour-related symptoms. Pooled analysis showed an effect of 1.27 (95% CI: 1.10 to 1.44), with moderate heterogeneity (I^2 = 53.8%, p-value = 0.043). Among other respiratory symptoms, nine studies reported exposure objectively, mainly with distance as a proxy of exposure. Only three studies reported significant findings for wheezing, asthma, and shortness of breath. Among studies evaluating exposure subjectively, eight reported significant health effects. Most consistent estimates were reported for asthma, while associations with wheezing were weaker. One study showed odour from livestock facilities related to difficulty breathing was significant (PR = 1.52, 95% CI: 1.02 to 2.27) and increased the lower respiratory diseases score (mean difference = 0.28, 95% CI: 0.05 to 0.5) for moderate/strong/very strong odour group. Moreover, people complaining about odour intolerance had a higher prevalence of self-reported respiratory infections (OR = 4.81, 95% CI: 3.24 to 7.14) or COPD (OR = 2.95, 95% CI: 1.84 to 4.73), and similar findings were found for the group with complaints about impacts on health vs. no complaints about COPD (OR = 2.05; 95% CI 1.21 to 3.49). People complaining about odours in terms of a health threat were found to be at a higher risk of enduring cough and COPD. Nonetheless, the precision of the effect estimate is lower in this sense. The included studies showed no association between odour and chest. Only two studies evaluated lung function and bronchial hyperresponsiveness. A reduction in PEF and FEV1 with increasing odour was found in both studies, however, 95% CIs included the null value. In addition, no associations were seen between self-reported odour annoyance and bronchial hyper-responsiveness to methacholine.

Upper respiratory symptoms and allergies

Ten studies presented data regarding associations between odours and upper respiratory symptoms. All studies were on adults. Only one study was conducted on workers.

Regarding studies with objective exposure, there were no consistent associations between distance zones and frequency of cold/flu, runny nose, nasal congestion and non-allergic rhinitis. On the other hand, within the studies with subjective exposure, a significant effect of odour with an increased risk for runny nose was found in only three. A borderline association was found between cold/flu and odour annoyance within last month (OR = 1.38, 95% CI: 0.97 to 1.99). In the only study conducted on workers, there were no significant differences between the flu score in exposed subjects and the control group.

Five studies evaluated the effect of odour on the immune system and allergic sensitization by estimating IgE and IgA concentration and an allergy score, but no association with increasing odour exposure emerged.

Mucous membrane irritation and skin disorders

Twelve studies evaluated odour effect on mucous membrane irritation. Six studies were conducted on skin disorders. All studies were on adults. No study was conducted on workers.

Six studies evaluated the occurrence of irritation symptoms objectively by distance zones. Significant odour effects were found related to prevalence of dry throat within the last 12 months, nose irritation, and skin irritation. When it comes to the studies that focused on subjective exposure, there were significant findings, with five studies pointing to eye irritation/burning eye, and sore/dry /burning throat (both odour tolerance and perception), two studies implying nose irritation/burning nose, nose/eye irritation symptoms were evidenced in one study, while three studies mentioned skin irritation/rash.

Mood states

Thirteen studies considered that malodour may have an impact in the mood states. All studies were on adults. One study was on workers.

Six studies evaluated exposure objectively. The only significant associations were reported for nervousness and difficulty concentrating.

Nine studies evaluated exposure subjectively. One study found significant associations for all mood outcomes, another one evidenced nervousness, angriness, stress, and

unhappiness. A third study found significant associations for sadness and stress-related symptoms. A dose-response association between odour annoyance and difficulty concentration was also detected. Additionally, workers in the high odour score group reported a higher post-traumatic score.

Cardiovascular system signs and symptoms

Three studies evaluated the effects of odour on cardiovascular symptoms and blood pressure. Each unit of odour increase on an 8-point scale was associated with increases in diastolic blood pressure (mmHg) (OR=1.26; 95%CI: 1.08 to 1.47), but not in systolic blood pressure. No significant association was found in the other two studies.

Odour nuisances

Ten papers investigated odour nuisances in the population regarding to their proximity to industries, odour perception, odour frequency or intensity, hedonic tone and NH_3 exposure. All studies were on adults. No study was carried out on workers.

Regarding studies evaluating exposure objectively, odour annoyance was in a significant association with odour frequency, with NH_3 concentration, as well as with modelled odour exposure. Moreover, three other studies showed a significant increase in odour nuisances in the closest areas to the odour source. A significant dose–response association with odour annoyance was found in one study evaluating exposure subjectively, which was consistent across the different exposure measure (odour frequency, intensity, hedonic tone), aggravating the effect in the severely annoyed subjects. In another study, the latter association was consistent across odour sources (livestock housings, slurry and manure, livestock farming in general).

Conclusion

In this systematic review and meta-analysis, we summarized the current knowledge on health effects of exposure to odour pollution from industrial sources. Several outcomes and surrogate endpoints have been examined in order to measure its effect and to assess its biological plausibility in the population object of study.

This study provides considerable support for the scientific conclusions adopted in The Distributed Network for Odour Sensing, Empowerment and Sustainability (D-NOSES) project and suggests additional suitable health outcomes to be associated with odour pollution. Among the major findings to date are the following:

1. Both residential and occupational exposure have been studied, nevertheless, only two studies involved an occupational exposure assessment in their study design, therefore, no conclusions could be made in this matter. Regarding the effects of residential odour exposure, even though a variety of estimates of the harms of odour pollution for health have been published and included in this study, evidence is still limited to potential effects of odour exposure in the health status of the exposed population.
2. Only 29 studies met the criteria of minimum methodological quality necessary for inclusion after an acute screening. Only 9 manuscripts were included in the quantitative synthesis.
3. 98 outcomes were reported at least once. Elevated prevalence of odour-related symptoms, such as headache, cough/phlegm, nausea/vomiting, wheezing and asthma, have been observed among the population exposed to industrial activities of the studies included. Given the lack of objective exposure and outcome assessment in the included studies, comparison of individual effects was limited, and results were mainly presented only descriptively.
4. The meta-analysis was only feasible to be conducted for 3 outcomes, observing a significant association between residential odour exposure and headache, cough/phlegm, and poorly associated with nausea/vomiting, which was of borderline statistical significance.
5. For other outcomes such as asthma/wheezing, mood states and mucus irritation symptoms, among others, there are reasonable grounds to believe that increased and prolonged exposure to odour pollution may be associated with a higher prevalence of asthma-related symptoms, mood-related signs and mucus irritation. At this point, it should be noted that the number of studies did not allow for a quantitative synthesis for these outcomes.
6. Regarding the quality of the included studies, and due to the fact that health outcomes were only based in self-reported information, potential sources of measurement errors limited our conclusions of dose-response patterns. In line

with previous critical reviews on this topic, our findings identified an evident mechanism relevant to biological plausibility of the association between exposure to odour pollution from industrial sources and the health status of the population.

7. This review fills a research gap because only one other review used a systematic approach to this field. The systematic review approach allowed for a delivery of a scientific literature synthesis that is valid, reliable and reproducible among professionals with relevant expertise, such as Cochrane Trial Search Coordinator. Moreover, different bibliographic databases were used to encounter odour-related health effects in the general population, and to evaluate the variability of studies assessing the odour impact from a wide variety of industrial sources. Additionally, the OHAT tool was applied to assess the quality of the included studies and the overall body of evidence. No gold standard is available for evaluating the quality of observational studies, especially in environmental health. However, this review shows that the OHAT tool could be helpful for this task.
8. The overall evidence is of "low"- "very low" quality, supporting the need for higher quality studies, especially regarding the study design (e.g., panel studies), the exposure assessment (e.g., dispersion models) and the outcome assessment (e.g., objective measures). In particular, the odour effect needs to be adjusted for the individual perception or annoyance; otherwise, the association could be biased. Most studies pointed out that odour annoyance and symptoms could be mediated by perceived odour and health risk and other person-related factors.

Introduction

Odour emissions from industrial sites constitute a major health issue for neighbouring residents and workers, mainly due to the olfactive nuisances that they engender (1-4). Even before the scientific knowledge about the air pollution's harmful effects was identified, it has been denounced for the annoyance it has caused. Nevertheless, most current research studies focused only on adverse health effects associated with pollutants identified from industrial sites instead of odour pollution. There is a variety of sources which produce odorous air emissions, such as wastewater treatment plants, livestock operations, composting facilities, landfills, paper and pulp mills or petrochemical industries, among others. Therefore, odour pollution is regulated by different approaches worldwide, and it is treated by policy frameworks either objectively or subjectively at a national or municipal level (2, 5). Despite the amount of research that has been conducted assessing odour impact on communities, a standard method to estimate odour concentration and evaluate effects on health has not yet been defined. Estimations of odour frequency, intensity and hedonic tone in the environment differ substantially among countries, according to their odour regulations (2-7). Although the overall impact on communities by odour emissions remains unclear, there has recently been a rising number of concerns and complaints regarding their possible serious health effects, which ended up increasing the quantity of studies performed on this topic lately(2, 3, 7, 8).

The olfactory function plays an important role in the detection of hazards in the environment, and it is usually the first point through which air pollutants enter the human body. Olfactory receptors of the nasal epithelium may detect odorant compounds inducing sensations in different ways. At elevated concentrations, odorant receptors may send signals via the olfactory and trigeminal nerve to the brain, causing different reactions, also known as subjective symptoms. Odour sensations processed in the central nervous system may induce pleasant reactions, positive moods and emotions, such as increased concentration or deeper sleep. On the other hand, unpleasant smells may cause negative responses including irritation, pain, sneezing, salivation, vasodilation…, ultimately resulting in nasal obstruction, bronchoconstriction, mucus secretion and inflammation (3, 8-11). Many authors considered malodours, mould or bad air quality as environmental triggers of headaches, eyes irritation, and unusual tiredness, among others (10). Even at very low concentrations, residents are likely to elicit mucous membrane

irritation. It is also important to note, that individuals' sensory responses can vary due to physiological factors, age or sex, repetitive exposure, perceived health risk, social factors…(9, 12-21).

Several studies measure odour annoyance and monitor community impact by self-reported somatic symptoms, as well as objective health effects, commonly including respiratory inflammation and dysfunctions diagnosed by a physician. When approaching odour assessment, surveys and structured questionnaires have traditionally been applied for collecting information about the population's characteristics and health status (6, 22).

It is challenging to measure ambient odour levels, primarily due to the nature of the exposure itself. Odour emissions are generally composed by complex mixtures of different volatile chemical compounds. Besides, the sensitivity of people and responses to odours are different among individuals, hindering efforts to monitor and assess their health effects. In view of the above, it is considered that odour analytical tools are too vaguely accurate (4, 21, 23-27). However, there are some predictive and observational tools that are often used to estimate odour exposure, such as atmospheric dispersion models, which predict hourly odour concentrations (ou/m^3) above the 90^{th} percentile (5, 28), distance to the source (6, 29-31), frequency of odour events per year, sniff tests (4, 31, 32), chemical compounds analysis (11, 33, 34), and sometimes complaints monitoring related to mean annoyance response or percent of highly annoyed residents (19, 29, 35-37).

Defining odour and odorants

In scientific terms, an odour can be defined as a mixture of substances generally at a very low concentration, such as small volatile organic compounds (VOCs), inorganic gases and peptide molecules, produced via multiple metabolic processes, which are emitted by organisms and other sources, and capable of stimulating the olfaction sense sufficiently to trigger a sensation (38-41). Odours are also referred to as "scents", which may be used to characterize both pleasant and unpleasant odours (42).

The perception of an odour initiates with a sniffing episode, consisting of several sniffs. The dictionary defines the word "*sniff*" as drawing up air audibly through the nose to detect a smell. It is considered as the physiological precondition of olfactory perception, and usually mentioned as a simple delivery method that transports odorous molecules to the odorant receptors of the olfactory epithelium, inside the nasal passage (38, 39, 43). In this context, an odour is described as an impression in the brain elicited by the recognition of a chemical by an olfactory receptor, or, in other words, the sensation that results from a perceived odour (38).

Consequently, a volatile molecule can be considered as an odorant when meeting the following requirements (38, 44):

1. It has to bind to an olfactory receptor.
2. The chemical interaction of odorant receptors with volatile molecules has to result in transforming into electrical signals that will carry the information about the odour to the brain.
3. The information transmitted to the brain has to be recognized so it can be interpreted.

The human sense of smell

Olfaction is one of the oldest senses, and it is of great importance for species survival. It has allowed communication between species from the beginning of life on earth. Organisms may identify food, potential mating partners, or dangers or enemies through odorant receptors. For many living creatures, such as humans, olfaction is one of the most important senses for interaction (38, 45-47).

Certainly, for primitive forms of life, which had very limited sound and optical impressions, chemical senses as olfaction were of essential importance in terms of both reproduction and food selection, especially when they were closely linked to the sense of taste. Development of brain capacity allowed primitive creatures to recognize and analyse different odours. Eventually, new stimuli in the environment endowed species with other capabilities. However, olfaction remains one of the closest senses greatly linked with the limbic system, which plays a major role in controlling mood, memory, behaviour and emotion. As Braise Pascal once said: "*The nose knows things that the mind does not understand"* (38, 45-47). Scientific literature associates the capacity of olfaction by the size of the olfactory system. Classic approaches considered that human olfactory organs diminished in size and function compared to the visual and the auditory system, which are considered of greater dependence for mankind (45). This misperception is a result of the fact that most of our conscious perceptions are transmitted via sight, hearing, and touch (48). Nevertheless, evidence claims that the mammalian olfactory system is one of the most evolved sensory system. Unlike other senses, such as vision and hearing, the number of discriminable olfactory stimuli remains unknown. Up until recently, the long-held belief was that the olfactory sense could only detect about 10.000 different odorants. In this context, odorants are typically mixtures of odour molecules that differ in their components, as discussed further in this manuscript (49). In comparison with other mammals, for example, canines were thought to possess approximately 20 times more olfactory receptor cells compared to humans (50). However, current lines of research contradict previous statements about the human sense of smell, claiming that it has a much higher capacity of odour discrimination. During psychophysical tests of odour mixture discrimination, *Bushdid et al.* found that the human nose is capable of discriminating at least 1 trillion different odours (51).

The importance of the human olfactory sense has been underestimated for years. Our olfactory receptors are directly connected to the most primitive part of the brain. In human biology and psychology, odours have the potential to influence our physiology and behaviour (51). The chemical senses (taste and smell) play a major role in eating behaviour, influencing stimulation of appetite, food choice, and food intake. Sensory cues based on a food's smell and taste trigger feeding-related reactions, for instance increased salivation. Although the association of odour exposure and the induction of appetite is not clear, it may also depend on other factors, such as intensity or odour identification, and hedonic tone or pleasantness of the individuals (52-54). Recent findings emphasize the strong impact of food cues on human physiology, which may also have further contributions to the obesity epidemic (52, 54, 55).

Another major property of the sense of smell is that it serves as a warning system to identify sources of potential danger (6). Olfaction is essential to detect and avoid potentially hazardous situations in daily life, such as gas leaks, smoke from a fire, and exposure to or ingestion of toxic substances (56-58). Individuals with impaired olfactory function are more likely to experience olfactory-related hazardous events compared to those with normal olfactory function.

A further common role of the olfactory system is mate recognition and sexual attraction. The importance of odours in the reproductive biology of some species is well documented. In 1959, *Karlson and Lüscher* first introduced the term of "pheromones" as chemical messengers that are emitted into the environment from the body of an individual and have the potential to influence physiological or behavioural responses in other individuals (59). Although it has always been pointed that humans essentially rely on visual and verbal cues when meeting with potential mates, the possible underestimation in this context has been largely discussed the possible too (60-62).

The sense of smell is essential for pleasurable social activity and happiness in life. According to the recent review by *Desiato et al*., about 20% of the population are estimated to be afflicted by anosmia or hyposmia (63). The inability or decreased ability to smell may have a severe impact on health and quality of life (QoL) (64-66). Significant poorer QoL has been associated with functional anosmia (46, 64, 65, 67, 68). Depression and loneliness have been associated with worse odour identification (64, 65, 69). Impaired odour identification is associated with increasing age (67); furthermore, it may

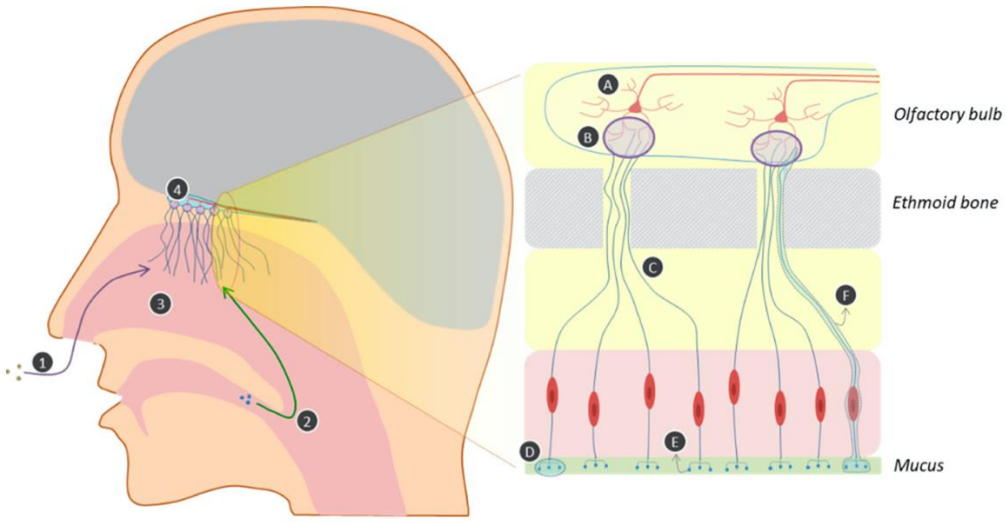
result from a decrease in cognitive abilities, as is the case for neurodegenerative diseases, but it has also been associated with chronic sinonasal diseases, severe head trauma, and upper respiratory infections (64). Recent studies also discuss the special features of odour-evoked memory and its role to induce emotional and physiological responses, which may improve health (70, 71). Olfactory disorders impair the ability to sense warning odours from potential dangers in food sources and the environment (72), as well as erode the quality of life in terms of interpersonal communication, eating, and emotional well-being (64, 65, 68).

Olfactory pathways

Humans are able to detect odours through the components of the olfactory system. The cortical areas of integration of the olfactory human sensations are very large, including olfactory peripheral structures (the olfactory epithelium), the olfactory cortex and the olfactory tubercle, some parts of cerebral tonsils, certain hypothalamic areas, the mediodorsal thalamic nucleus and the orbitofrontal cortex (45). Similar to other sensory systems, olfactory information is transmitted from the olfactory epithelium to the olfactory cortex and other parts of the brain in order to reach sensory awareness and trigger autonomic responses involved in appetite, salivation, and gastric contraction, among others (46, 73).

The mechanism of olfactory recognition can be divided into four basic steps: airflow of the odorants, binding to olfactory receptors, odorant transduction, and information processing and interpretation (Figure 1) (73, 74).

Figure 1. The Physiology of Olfaction



1. Orthonasal olfaction; **2.** Retronasal olfaction; **3.** Nasal cavity; **4.** Olfactory bulb; **A.** Mitral cell; **B.** Glomerulus; **C.** Axon; **D.** Cilia; **E.** Olfactory receptor; **F.** Olfactory Receptor Neuron (ORN)

Source:(73)

The olfactory epithelium occupies about 9-10 cm^2 of the roof of the nasal cavity (75). Odour molecules can reach the main olfactory epithelium via either of two paths, through "*orthonasal olfaction"* (direct inhalation from an external source through the nares), alternatively, via "*retronasal olfaction"* (through the throat when the tongue pushes air to the back of the nasal cavity during consumption, chewing or drinking) (73, 76).

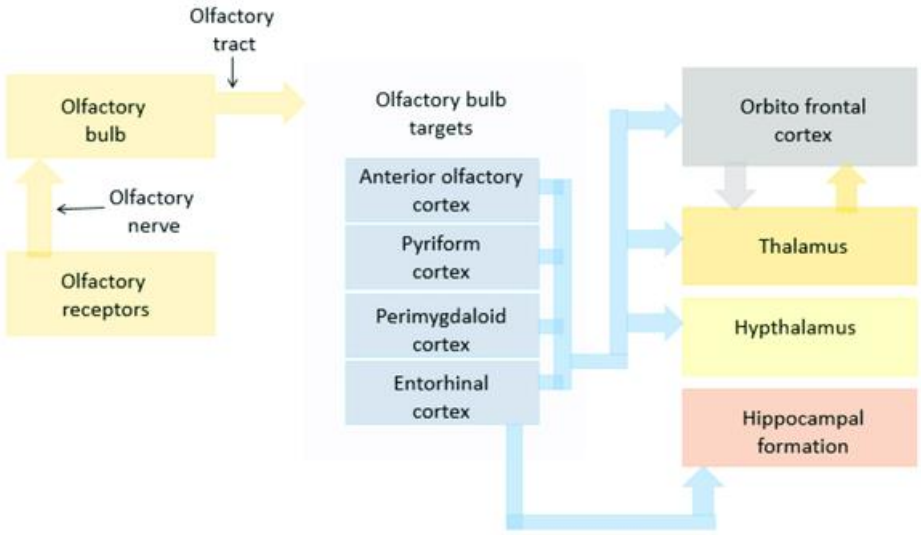
Receptor activation is one of the initial steps of a long chain of events involving olfactory recognition. The olfactory epithelium is composed of three major cell types: basal stem cells, olfactory receptor neurons (ORNs) and sustentacular or supporting cells (38, 77, 78). The odorants are detected by the ORNs in the olfactory epithelium, which is covered by mucus and contains olfactory glands. VOCs must penetrate the aqueous mucus layer of the nose to reach receptor sites on the olfactory cilia (38, 49, 73, 77, 79, 80).

Humans have approximately between 10 and 20 million ORNs within the olfactory epithelium in both nasal cavities (73, 74, 81, 82). The olfactory receptors are responsible for the initial detection of the odour molecules and the sensory transduction (38). Odorant transduction is the process by which the information related to the odour detected by the ORNs is transmitted through signalling pathways to the brain. Transduction begins with odorant binding to specific olfactory receptors on the external surface of the cilia; it is commonly referred to as the first stage in the olfactory process (43, 49, 77, 79, 80). Once an odour molecule binds to an ORN, it initiates an electrical signal that travels through the axon to the nerve fibres situated at the back of the nasal cavity. The axons of ORNs pass through the ethmoid bone to form glomeruli. Within each glomerulus, the axons of the ORNs contact the dendrites of mitral cells so synapses form onto projection neurons (46, 73-75, 79, 80, 82, 83). In humans, around 8000 glomeruli and 40 000 mitral cells have been counted in young adults forming the olfactory bulb (83). The olfactory bulb, also described by the scientific literature as the primary olfactory cortex, is a bilateral structure that lies on the cribriform plate of the ethmoid bone on the ventral surface of each frontal lobe, and it is the only relay before the signal is transferred from the periphery to other brain areas for additional processing (38, 77, 81).

Following this, the mitral and tufted cell axons form a bundle, the lateral olfactory tract, that carry information to the olfactory cortex, consisting of several areas also known as secondary olfactory regions, including the anterior olfactory nucleus, the olfactory

tubercle, the piriform cortex, the entorhinal cortex and some portions of the amygdala (Figure 2) (38, 77, 81).

Figure 2. Schematic illustration of the basic pathways for processing olfactory information



Source: (77)

Finally, projections from the secondary olfactory cortex will be transferred to higher levels of the Central Nervous System (CNS), the tertiary olfactory regions, which include the orbitofrontal cortex, several thalamic and hypothalamic nuclei, the hippocampus and additional subnuclei of the amygdala. Here, the signal is decoded and interpreted so that olfactory responses may occur (38, 74, 77, 81). The orbitofrontal cortex is a portion of the prefrontal cortex region that is located on the underside of the frontal lobe and situated immediately above the eyes orbit, simultaneously encoding both the value and the identity of the odour information (see below, *Odour characterization*, for a detailed review on olfactory identification) (38, 46, 79, 81). Lesions in this region may result in an inability to identify and discriminate different odours. Odour information is also sent to portions of the hypothalamus and brain stem nuclei that trigger autonomic responses through the parasympathetic nervous system (PNS) involved digestion, such as appetite, salivation, and gastric contraction (79).

Olfactory perception

The sense of smell is of significant importance in evolutionary terms, and it is considered as one of the major ways of interaction with the environment (45). Recent scientific literature indicates that the olfactory sense is home to millions of ORNs and approximately a thousand genes encode and transmit features of the olfactory stimulus, which allow humans to detect and discriminate infinite number of odours and odour combinations (79, 84). It is nevertheless important to highlight that only a relatively low number of olfactory receptors are enough to recognize around thousands of different odour molecules (38, 51, 84-86).

Olfaction may be affected by a large number of factors, including genetics, gender, age, health and environment, and may vary in both general olfactory acuity and the perception of specific odours (79). Human odour perception represents the physiological reception and the psychological interpretation of a specific odour, although, it can be generally defined as the ability to detect and recognize an odour (81, 87, 88). It should be noted that the percept of an odour displays tremendous variability among individuals, including differences in odour detection threshold, quality, intensity, and pleasantness (79)(see *Odour characterization*).

In human physiology, the percept of an odour begins with the stimulation of ORNs on the roof of the sinus cavity, leading to the generation of a nerve impulse in the olfactory bulb, and terminates in higher cerebral centres which, when activated, make us consciously aware of an odour (84). Volatile odorous compounds induce emotional responses that can range from extreme disgust to extreme pleasantness, even if an olfactory stimulus is not consciously perceived (79, 84). Despite the evolution of previous primitive organisms and the development of human brain capacity, the perception of an odour remains closely connected to our limbic system (see *Olfactory pathways*), a brain region which is an essential substrate of emotional, social and sexual behaviour and memory response of the body (38, 89).

From initiating investigations to the most recent scientific literature, the response to odours has been often related to past memories and cultural experiences (81, 84, 87, 88, 90, 91). Nowadays, one of the most fascinating features of our sense of smell remains in its odour-evoked memory capacity, both eliciting emotional responses and motivating

behaviours. Trygg Engen was a pioneer in the field of odour memory, developing the fundamental mechanisms of olfactory perception and cognition in his book *The Perception of Odors (1982),* which allows the understanding of the uniqueness of our odour memory system, even forty years later. (90).

As mentioned earlier, it is known that different people may have remarkably different odour responses, depending on social characteristics, such as their culture or sex (91, 92). Correct odour identification requires integrating enough sensory information from certain odours, which are able to cue memories, recognizing the odour as familiar, and retrieving an odour name, forming the odour-word relationship (64). According to *Ferdenzi et al*. 2016, names of odours may increase their ratings of familiarity, pleasantness and edibility. Moreover, it may decrease or impair cultural differences when the names are provided (91, 92).

Overall, different people find different odours unpleasant at different concentrations, which is frequently related to the way people perceive odours. The perception of an odorant depends on both the characteristics and concentration of the odorant, and the characteristics of the person who is smelling the odour, as explained later on. (93-98).

Odour characterization

The interaction of volatile chemicals compounds inhaled through the nose produces the odour sensation. Chemical compounds may vary in their ability to produce an odour sensation. The perceptibility of an odour (whether you notice it or not) is one the primary characteristics. However, the exposure cannot be quantified by the detection of an odorant, nor the negative health implications of being exposed to a certain amount of volatile chemicals. Further dimensions may be as essential in other to characterize an odour (38, 41, 93, 99, 100).

The sensory perception of odorants can be may be characterised by the following major components:

Odour detection threshold (ODT). It represents the smallest value of the concentration at which any specific odorant may be perceivable by human olfactory receptors. It is also defined as the concentration at which a specific odour produces a sensation. It provides a quantitative assessment of the effect of an odorant on the olfactory system. It is the basis of olfactometry, as a standardized quantitative measurement used to define concentrations of an odour (39, 41, 99-102). According to the European Standard EN 13725:2003, the odour concentration is expressed in European Odour Units per cubic metre (OU_E/m^3), which represents the number of repeated dilutions evaporated into one cubic metre of neutral (odour-free) air that are needed to elicit an odour response from a 50% of a panel of selected trained observers, in other words, to bring the concentration of the sample to its ODT (4, 38, 94, 100, 103-105). The odour concentration is statistically equivalent to the dilution factor of the detection threshold: e.g., to put it in simple terms, an odour sample with a concentration of 100 OU_E/m3 means that the odour sample has been diluted a hundred times with clean air to reach the panel threshold, so that the panel cannot perceive the odour anymore (4, 100).

At the detectability threshold, there are many other attributes available to complete this definition. On one side, the ability to distinguish between odours is called "*recognition threshold*" (RT), expressing the first concentration at which an individual may identify the odour source. Furthermore, "annoyance threshold", which represents a key feature for measuring and reporting detectability and is defined as the concentration at which a volatile substance is capable of provoke a sensation of annoyance (38, 99). Finally, there

is one last attribute, “Odour activity value” (OAV), often used to know the ‘weight’ of perception of an odorant. This is calculated as the ratio between the concentration of an individual substance and the threshold concentration of this substance (94).

Olfactory threshold varies between individuals, but it also fluctuates greatly during the day, as well as from one day to another for the same individual. It is strongly influenced by internal factors, like state of health or age, but also external, such as the presence of interfering odorants, or duration of the exposure. The smaller the ODT, the higher the odour sensitivity.

Intensity. It can be defined as the individual’s perception of the strength of the olfactory stimulus, or rather, the way in which a subject perceives the magnitude of a mixture of odorants once it is above its threshold (93, 102). It is related to the concentration and expressed by the logarithmic function of the concentration of the odour, as represented by Weber-Fechner’s law (Figure 3) and Stevens’ law (Figure 4) (38, 100, 106-109).

Figure 3. Correlation between the intensity of the olfactory stimulus (I) and odorant concentration (C) according to the Weber-Fechner’s model

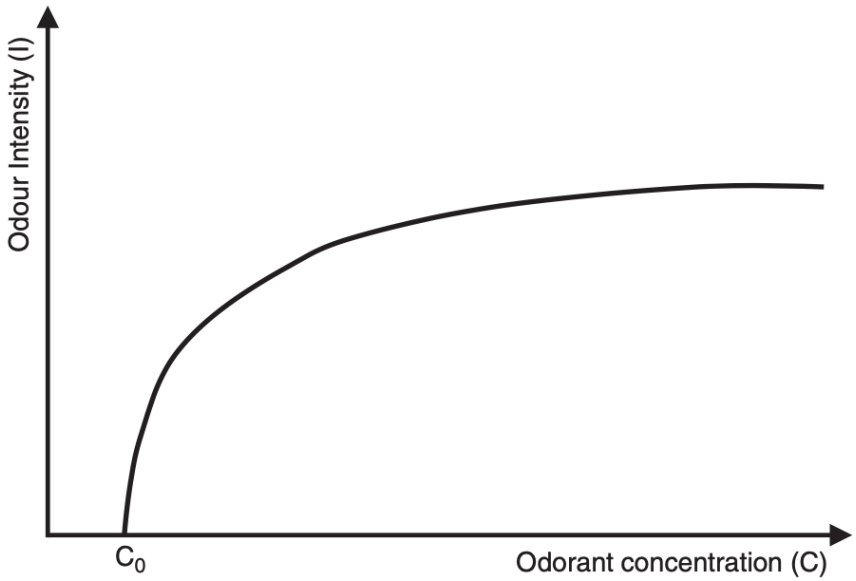
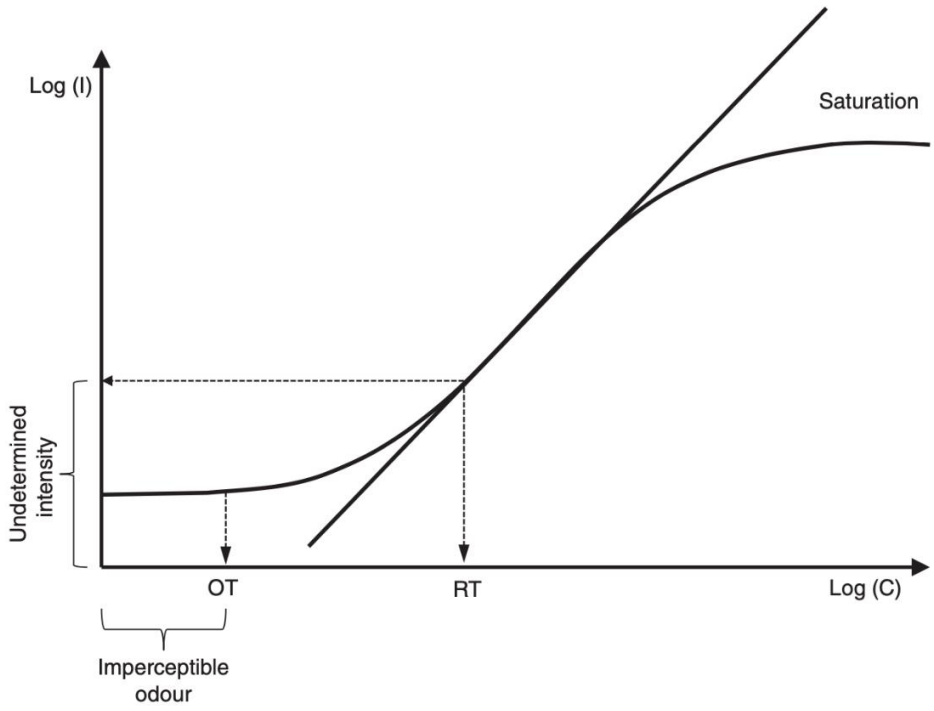


Figure 4. Correlation between the intensity of the olfactory stimulus (I) and odorant concentration (C) according to Stevens' model (OT: odour threshold; RT: recognition threshold)



Although traditional quantitative measurements are largely extended, there are also subjective scales for grading odour intensity. Here, the odour intensity is divided into different categories. A 7-point standard scale was proposed by the Association of German Engineers (VDI), where a panel of trained observers determined the magnitude of an odour perceived ranging from faint to strong according to the magnitude of odour perceived by each one of them (Table 1) (110, 111). The perceived intensity of an odour increases as concentration increases, but the relationship is not lineal but logarithmic, as mentioned above (100, 102).

Table 1. Odour Intensity Scale

Score	Odour intensity (I)
0	Not perceptible
1	Very weak
2	Weak
3	Distinct
4	Strong
5	Very strong
6	Extremely strong

Diffusivity. An odour can only be perceived when a gaseous molecule reaches the olfactory epithelium. The diffusivity of an odour is defined as the degree of volatility of odorous substance. This attribute is essential to estimate how far a volatile chemical can spread and cause an odour sensation. Therefore, an important characteristic is the chemical's vapour pressure, which indicates the chemical's tendency to volatilize; it is a parameter of odour diffusion capacity (38, 41, 89, 100, 102). Odour diffusion capacity can be evaluated by estimating the Odour Index (OI) which represents the ratio between the vapor pressure of the substance (ppm) and the OT at 100% (ppm) (89, 112):

$$OI = P_{vap}/OT_{100\%}$$

The OI does not provide information about the pleasantness and unpleasantness of a particular smell, which is linked to the hedonic tone. A key parameter of the diffusivity of chemicals is the pervasiveness, which reflects an odour's staying power. In other words, it represents the ability of some substances to diffuse upwards more than other, impacting more on the surrounding areas (89, 112).

Hedonic tone (HT). It is a measure of the pleasantness or unpleasantness of an odour. This parameter is a subjective measure of the acceptability of an odour and a key element in estimating odour annoyance (17, 41, 100, 102, 113-115). As most parameters, the HT is not an independent quality of a volatile compound, and it depends on the intensity, concentration, duration and frequency of the odour exposure (95, 96). Moreover, the HT also differs widely from person to person, and it is strongly influenced by previous experiences, emotions and other circumstances. The HT can be rated on a judgement scale of the relative pleasantness or unpleasantness. According to the German guideline VDI 3882 (97, 98, 108, 109), the methodology uses a nine-point scale, ranging from *-4* (extremely unpleasant) to *+4* (extremely pleasant), being *0* an odour that is perceived neither as pleasant nor unpleasant (Figure 5-6).

Figure 5. Category scale for the evaluation of hedonic odour tone

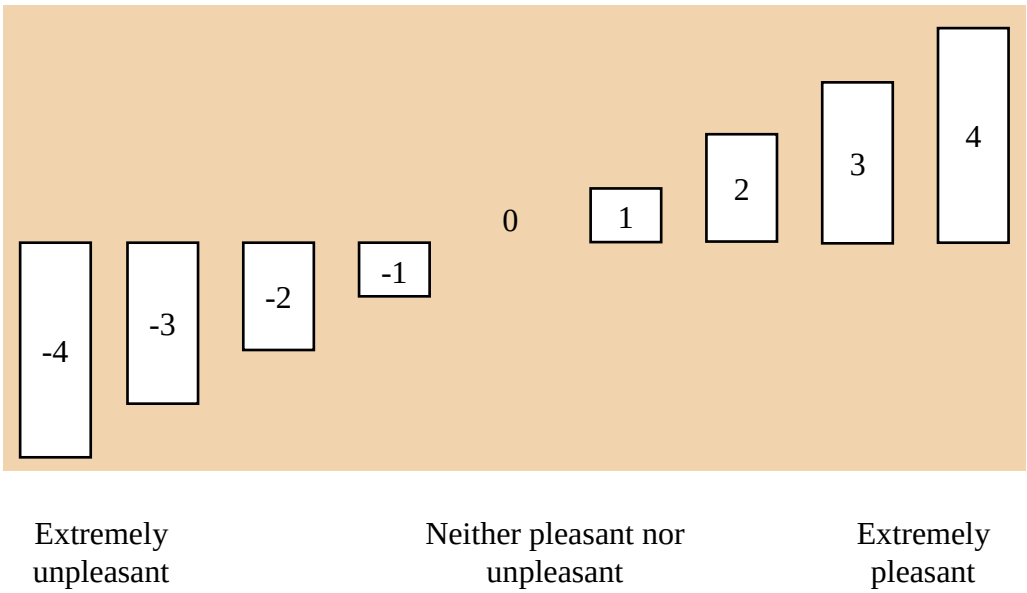


Figure 6. Example of a data record form of a nine-point scale of hedonic tone.

Data record form – odour hedonic tone

Please describe your odour hedonic impression for the quality ***odour source (e.g. backery odour)*** with the following scale:

most pleasant impression

extremely unpleasant				neither unpleasant nor pleasant				extremely pleasant
❍	❍	❍	❍	❍	❍	❍	❍	❍
–4	–3	–2	–1	0	+1	+2	+3	+4

most unpleasant impression

extremely unpleasant				neither unpleasant nor pleasant				extremely pleasant
❍	❍	❍	❍	❍	❍	❍	❍	❍
–4	–3	–2	–1	0	+1	+2	+3	+4

mean impression

extremely unpleasant				neither unpleasant nor pleasant				extremely pleasant
❍	❍	❍	❍	❍	❍	❍	❍	❍
–4	–3	–2	–1	0	+1	+2	+3	+4

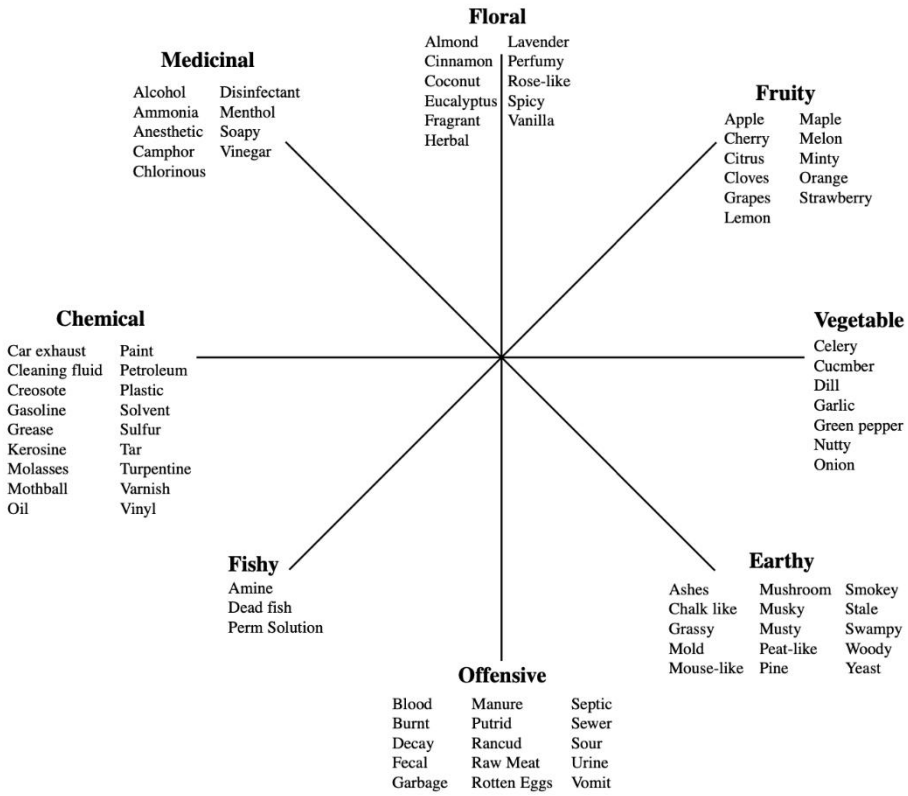
Source: (100, 108, 109, 116)

Furthermore, it should be noted that it is not sufficient to evaluate the acceptability of an odour by simply referring to its hedonic tone. Individual characteristics such as ODT have a strong influence in the odour's acceptability, together with cognition (perceived

environmental risk, expectations of illness, toxicity, opinions in society) and coping, which are factors involved in the process (95, 96).

Quality. It defines the odour's specific character, allowing the identification of its type. It is basically what the odour smells like and it allows to discriminate between odours. There are numerous standard methods to characterize odours through multidimensional scaling or profiling, consisting of a list of sensations and descriptors, which allows to relate the odour to others that are familiar or widely recognized. There are eight recognized odour descriptor categories (vegetable, fruity, floral, medicinal, chemical, fishy, offensive and earthy), which are illustrated as an "*odour wheel*" with a list of specific descriptors within each category (Figure 7) (38, 41, 100, 102). A table with the resulting mean hedonic tones of each descriptor was listed by *Dravnieks et al*. (1984) (113).

Figure 7. Odour descriptors wheel by McGinley et al.



Source:(117)

Odour measurement methods

The impact of odours on the surrounding areas depends on many factors, such as the amount of odours emitted from the odorous site, the distance from the odour source, weather conditions, topography, plus some person-related factors associated with odour perception, like odour sensitivity and tolerance of the citizens, as mentioned earlier in this manuscript (*Olfactory perception*; *Odour characterization*).

Several techniques have been developed for the characterization of environmental odours originating from industrial activities, with the purpose of assessing its impact on societies. There are different approaches for measuring odours, which simulate its dispersion in the atmosphere. Odour measurement methods may be divided into three categories based on the type of approach: mathematical methods, instrumental measurements, and sensorial measurements. Furthermore, odour impact assessment may be applied at the emission-level, at the odour source, or a receptor-level, where the citizens are located, and the complaints come from (4, 24, 25, 41, 100). Table 2 proposes a classification scheme on the existing techniques for odour impact assessment.

Table 2. Overview of odour impact assessment methods, according to measurement type, and from the emission (odour source) or the immission (receptors' perspective) point of view

	MEASUREMENTS		MATHEMATICAL METHODS
	Sensorial	Instrumental	
EMISSIONS/ SOURCES	Dynamic olfactometry (EN13725:2003) Gas-Chromatography-olfactometry (GC-O)	Chemical analysis • With speciation (GC-MS) • Single gases • Non-specific Electronic nose (IOMS)	Odour Emission Factors (OEF) Emission databases
IMMISSIONS/ RECEPTOR	Field Inspection (EN 16841:2016) Field olfactometry Citizen Science (recordings from residents)	Chemical analysis • With speciation (GC-MS) • Single gases Electronic nose (IOMS)	Dispersion models (Gaussian, Lagrangian and Eulerian model)

Source: compilation based on information supplied by (4, 24, 25, 41, 100)

Below is an overview of the most common technical approaches to odour measurement and to simulate its dispersion in the atmosphere. On the one hand, sensorial and analytical measurements are used to assess odour concentration, using a panel of trained people or instruments. Likewise, air dispersion modelling assesses the impact of odour pollution on receptor-level using meteorological, topographical and emission data.

Sensorial analysis

Odour sensorial techniques are based on the human perception capacity (4, 24, 25, 41, 100). The mammalian olfactory system, which developed over millions of years, is one of the most evolved sensory systems, whose high sensitivity and complexity allows it to discriminate between thousands of different odours (118). Sensory measurement techniques may be divided into two categories, quantitative and qualitative assessment, depending on whether they couple the human sense with or without instrumentation (24, 25). Sensorial techniques include dynamic olfactometry, gas-chromatography-olfactometry, field inspection, field olfactometry and citizen science.

The **dynamic olfactometry (DO)** has become the most widely applied objective method for assessing the odour impact by measuring the odour concentration at emission-level using the human sense of smell. It is a sensory measurement which employs the human nose as the odour detector, and it is useful for making comparisons of odours from different sites, in compliance with the principles of objectivity and reproducibility. The measurement of the odour concentration is made using a dilution device, named olfactometer (figure 8) (4, 24, 25, 41, 100, 103, 119-122). First, samples of odorous air are collected in suitable bags, normally in 10-litre *Tedlar* ® or *Nalophan™* bags (119, 123), from the odour site, and analysed thereafter. Samples are diluted with neutral air (odourless air) at different concentration levels through the olfactometer, which releases the air in a controlled way to a panel of selected people with a standard sense of smell, "*sniffers*", and trained following the European Standards (EN 13725:2003) (see *Odour regulations*). Panellists are selected after satisfying the following requirements based on the *n-butanol* test. According to Van *Harreveld et al.*(124), and European Standards (EN 13725:2003), each participant must be able to detect a reference odorant (n-butanol)(24, 25, 94, 119, 123, 125):

- Average n-butanol ODT between 20 and 80 ppb over at least 10-20 tests.

• The standard deviation of individual responses needs to be below 2.3.

Figure 8. Panel of selected people applying the DO method

Source: International Odour Observatory

In order to evaluate answers recorded by the panellists, a statistical analysis is usually required to obtain results. The outcome of this measurement is the odour concentration determined by the panellists, and it is expressed in OU_E/m^3 (ODT; *Odour characterization*).

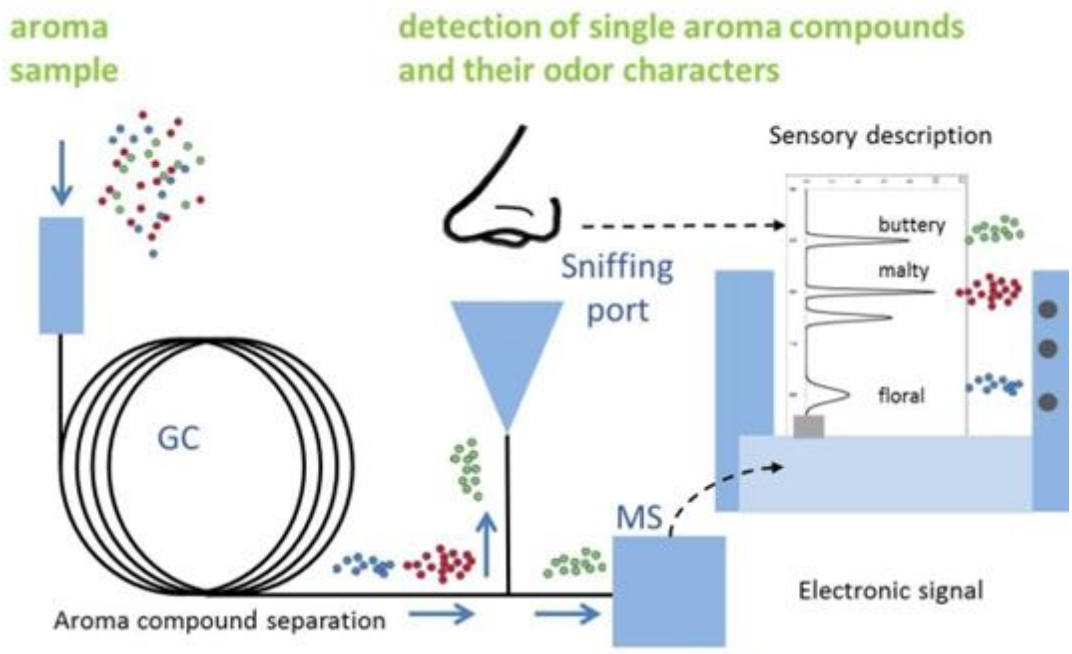
It should be noted that data recorded by dynamic olfactometry may be used as input data for dispersion modelling (25). Some of its limitations include discontinuity of the odour measurements, and lack of information to estimate the odour quality. Moreover, dynamic olfactometry neither allows to differentiate between odours, nor to estimate odour impact at receptor-level (41). Field olfactometry is a technique intended for odour impact assessment in cases in which lower values of odour concentrations start in a range of 50–100 OU_E/m^3, even though limits vary depending on the olfactometer, as well as on the baseline odour of the sampling bags used to collect the air samples. The method is not applicable for low odour levels. Field olfactometry or field inspection should be used instead (105, 126).

According to the EN 13725:2003 (94), the fundamental application of the olfactometry is "*to provide a common basis for evaluation of odour emissions in the member states of*

the European Union." In this sense, dynamic olfactometry may be used to ensure that regulations about concentration limits are being met.

Gas-Chromatography-olfactometry (GC-O) combines a GC system equipped with an olfactory detection port. From a sniffer mask, the trained panellist smells the gas and provides information about the aroma. Previously, the GC column has separated the chemical compounds of the gas mixture that later on would be presented to the panellist separately with equal flux in order to detect the presence of the odour (figure 9) (127, 128). GC is able to evaluate the duration of the odour episodes, to describe the quality of the perceived odour and quantify its intensity (127). GC-O is an objective technique able to identify the odour source and characterize single odorous compounds responsible for the odour annoyance. The objectivity of the technique makes its implementation to atmospheric dispersion models possible (25, 41, 122, 127, 128).

Figure 9. GC-O diagram



Source: (41)

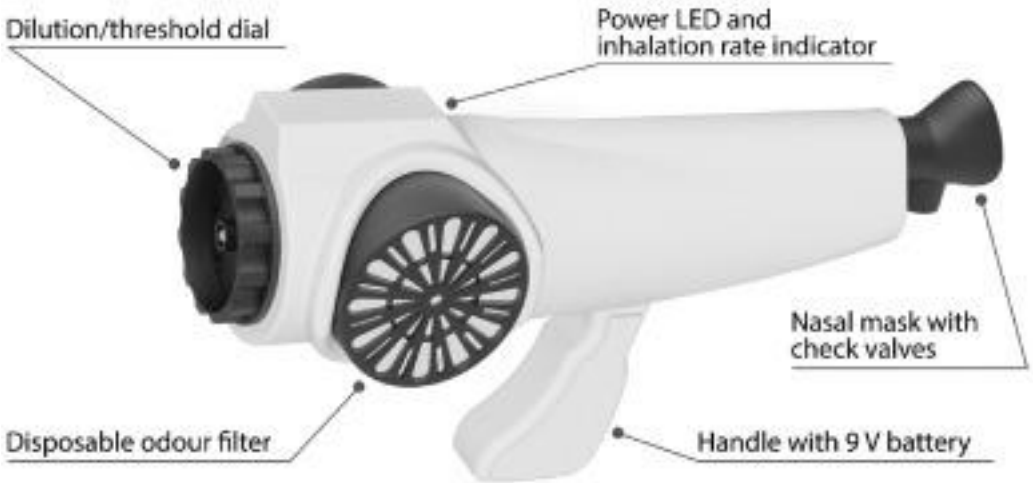
The **field inspection** uses the human nose from a panel of selected people trained to assess the presence of odours directly in the field. It is based on a number of visits within a defined assessment area (field) by panellists, who identify and record the presence or absence of an odour. The field inspection uses the frequency of odour episodes in terms

of odour hours; an odour hour is defined by at least 6 minutes of detectable odour concentrations (24, 25, 41, 122, 126, 129).

The field inspection technique was first regulated by the VDI Guideline 3940-Part 1 and Part 2, 2006 (130, 131). Moreover, the method has been recently standardized by the European Union by EN 16841:2016, based on the pre-existing German Standards. The European Standards distinguish between two different approaches: Grid and Plume method (EN 16841-1, 2016, EN 16841-2:2016 2016) (97, 98). The grid method uses direct assessment of the ambient air by human panel members to characterise odour exposure in an area of interest over a long period - usually one year - to include different meteorological conditions of that location. The plume method is based on the estimation of the extent of the downwind odour plume of an industrial facility by a group of panellists, under specific meteorological conditions, including specific wind direction and speed, and boundary layer turbulence (41, 122).

Field olfactometry (FO) consists of using portable devices (figure 10) that create a series of discrete dilutions by mixing odorous air with neutral air (odourless air) by trained panellists. A group of panel members move to an area of interest (odour source) and use the device to measure the "*Dilution-to-Threshold*" ratio, which is the period of time the air needs to be diluted before it may no longer be detected by the human nose. Data obtained by FO do not provide an odour concentration in OU_E/m^3(24, 41, 105, 122, 132).

Figure 10. Field olfactometer



Source: (105)

Citizen science (CS) involved the participation of communities in recording the frequency, intensity and type of the odour. It is based on reporting cards filled out by residents living in the vicinity of the odour source. The data obtained from social participation may be associated with other parameters, such as meteorological data recorded during the same study period, allowing its integration and comparison to dispersion models. Limitations are based on the subjectivity of the data due to person-related factors and characteristics, for instance, psychological effects of the population involved. Seeing that the participants are not trained as panellists, data variability in the recordings must be taken into consideration. Finally, CS does not provide odour concentration in OU_E/m^3, which is only measured by the DO at emission-level (25, 41, 122).

Instrumental or chemical analysis

Recently, the possibility of applying instrumentation for the identification and characterization of environmental odours has become a topic of great interest. Instrumental analysis is based on the evaluation of the chemical composition of air. The techniques developed for this purpose are chemical analysis of single gases, gas chromatography coupled with mass spectrometry, and electronic nose.

Chemical analysis of single gases involves assessing the concentration of a single compound, such as ammonia (NH_3) or hydrogen sulphide in ambient air, which may be a proxy of the odour impact of the area exposed to the substance. It is only applied when there is a previous evidence of correlation between the volatile compound and the odour concentration in the area of interest. Some of the limitations are related to its inadequacy in case of mixtures of many odorants, its dependence on the instrument and the sensor used for the measurements, and inability to recognize the source of exposure (13, 14, 41).

Gas Chromatography coupled with Mass Spectrometry (GC-MS) is a method that couples GC and MS techniques, amplifying their potential and allowing the complete identification and quantification of the individual volatile compounds present in an odour sample with lower detection limits. The volatile compounds are separated in the GC column, due to the different affinity of the molecules to the column package, and their reach of the end of the column at different retention time (elution times). Components are qualitatively identified based on their retention time, and then quantitatively characterised

by their mass-spectrum using the mass spectrometer. Historically, it was the first method developed particularly for odour measurements, however, its main limitation arises from the lack of information from the human perception. Furthermore, detection limits are often below the odour detection threshold of the odorous air compounds. Advantages from GC-MS include its robustness, low detection limits, high accuracy and the ability to identify single substances in a mixture (24, 25, 41, 119, 122).

Electronic nose (E-nose) is a scientific device which simulates the receptors of the human olfactory system in the detection and characterization of odours. The chemical volatile compounds react with the surface of the sensors by means of physicochemical interactions, so subsequently the recorded information can be processed by computer programming, simulating the response of the human brain. For this to work, the e-nose must be previously provided with a database of air samples relating to the odours to which, the e-nose will be exposed to in the analysis. This method allows a continuous and direct determination of the presence/absence of odours, the determination of the origin of the odour (source), and the possibility of comparison between other odour measurements (24, 25, 41, 122).

Mathematical methods

Recent, publications have applied atmospheric dispersion modelling to the assessment and control of odours, instead of the traditional methods described previously. Dispersion models are normally classified with regard to their spatial scale (local, local-to-regional, regional-to-continental, global) (105). The dispersion may be mathematically described using equations, such as the originally Gaussian form model (Industrial Source Complex, Keddie, 1980) Additionally, they can and simulate the dispersion of air pollutants into the atmosphere (122, 133). Gaussian models are the most common air pollution model, often used for regulatory purposes. The dispersion process initiates when air pollutants are discharged into the atmosphere, carried along by the wind and diluted by the turbulence. As the exhaust gases and pollutants leave a stack, they mix with the ambient air describing a plume. The plume diameter progressively grows, and it spreads and disperses. Since Gaussian models assume a homogeneous wind field, it is not recommended that they be used for modelling under low wind conditions, or at sites close to the odour source. According to the scientific literature revised, Gaussian, Eulerian and Lagrangian models are frequently used for modelling odour immissions (122, 129, 134).

One of the disadvantages of dispersion modelling, apart from its complexity, is that the input data are often vague (odour concentration, volume stream, representative meteorology, dispersion specific parameters). In addition, the information of the location's meteorology is often limited. For that reason, odour dispersion models often combine information from sensorial and instrumental odour measurements, allowing for a better understanding of the odour annoyance and its characterization (25).

Even though dispersion modelling may be considered as a more convenient technique for measuring odour, there is still limited evidence on studies which assess dispersion model reliability, particularly regarding odour - only a few concerning this matter have been published up to now (134, 135). Moreover, there is a further difficulty in this matter, which is that air dispersion models quantify the concentration of odorous compounds and VOCs, but current models do not account for effective human odour perception very frequently (25, 122).

Environmental odour pollution

Odour pollution and environmental air quality are topics of major concern worldwide, especially when the industrial facilities are located very close to inhabited areas. As it was noted previously, unpleasant odours may be a warning sign of potential dangers to human health. When normal exposure limit concentrations are exceeded, most conventional pollutants are not perceived by the population. On the contrary, people will often notice an odour before they are at harmful levels, due to the low ODTs (concentration) of the odorous compounds (4). Furthermore, National and Local Public Health Authorities have reiterated on countless occasions that odorous air emissions affect the quality of life and wellbeing of the population (41, 136).

According to the European Environment Agency (EEA), only preceded by noise, odour pollution is considered one of the most common causes of environmental complaints, which would decline quality of life of the population that may be affected by them. Certainly, the effect of odour pollution must be addressed in the context of health and well-being, especially given the holistic nature of the concept of health (38). Here, it is necessary to recall the World Health Organization (WHO) definition of health (137):

“Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”.

Clearly, industrial odour pollution remains one of the biggest sources of complaints within communities. However, effects of health depend on a variety of each individual, such as their age, sex, medical condition, odour perception, hedonic tone (pleasant/unpleasant), odour sensitivity and tolerance. Moreover, the impact of odours depends on several environmental factors, such as intensity and type of substance aerosolized in the environment, the distance from the odour source, weather conditions and topography (6, 25, 138).

There is a mixture of different volatile chemical species, which are responsible for odour episodes of varying degrees of nuisance. Odorous air emissions from anthropogenic origin may be emitted from a variety of municipal, agricultural and industrial activities comprising different economic sectors (138):

- Municipal odours sources include wastewater treatment plants (WWTP), storm drain systems, municipal solid waste (MSW) composting.
- Agricultural odours sources include animal husbandry (livestock feedlots, also known as concentrated animal feeding operations (AFOs), slaughterhouses, poultry farms) composting and other biomass operations, and pesticide operations.
- Industrial odour sources include paper and pulp facilities, geothermal power stations, petrochemical refineries, foundries, bakeries, breweries, rendering plants, metal degreasing and painting operations, and hazardous waste sites, among others.

Odour regulations

As it has been acknowledged in previous chapters of this manuscript, for several decades, it has been known that odours resulting from industrial activities may have adverse effects on citizens. Many of the odour emissions that we encounter daily are increasingly relevant for Public Health Authorities, in terms of odour nuisances. Consequently, over the last years, there has been a noticeable increase in the number of regulations on environmental odours worldwide, particularly at the European Union (EU) level and at a national level by each country member (38, 103, 139).

According to the Directive 2010/75/EU on Industrial Emissions (140), European countries shall take all necessary precautions in order to prevent and limit air, soil and water pollution, as well as negative environmental effects, such as odours and direct risks to human health. It is clear that the appropriate objectives need to be set for controlling ambient odour levels, independently of the measurement method used. There are different approaches to regulating odour emissions, and they may be classified into the following categories:

1. Regulations based on air quality standards and limit values. Here, levels of action include:

- Setting qualitative limits on odour emissions, allowing local authorities to close a facility because of its odorous emissions (when the odorous air becomes unacceptable).
- Setting minimum distance standards from the closest inhabited area where odour-producing industrial facilities may be located.
- Setting maximum emission standards on odour emissions, expressed by odour concentration. In this matter, the European Standards EN 13725:2003 and EN 16841:20016 (Part 1 and Part 2) and the German Standards VDI 3880:2011 recognized standards for emissions sampling and analysis techniques (*Odour characterization*) (94, 97, 98).

2. Regulations on direct exposure assessment. Here, odour emissions are regulated based on maximum impact criteria measured mainly by dispersion modelling (122, 133). The assessment of ambient odour at receptor-level allows to limit emissions where a very

special air quality protection is required. Alternatively, field inspections and citizen science may also be applied in this category (*Odour measurement methods*).

3. Regulations based on "no annoyance". Here, directives and regulations focus on the Maximum Annoyance Standards (MAS). MAS are based on the relationship between environmental odour exposure and health-related complaints, which is mediated by odour annoyance. To estimate the level of population annoyed, surveys and questionnaires may be carried out, rating the level of perceived annoyance on a scale (e.g., a 5-point scale ranging from "not annoyed" to "extremely annoyed").

4. Regulations based on the application of best practice. Here, directives aimed at linking legislative and regulation processes closer to empirical evidence, also known as evidence-based policymaking. Regulations based on best practice may be defined as the systematic application of tools (any law, regulation, rule, procedure, decision, policy or administrative action) to ensure that regulatory outcomes are effective, transparent, inclusive, and sustained.

Regulations, standards and guidelines covering industry-related odour pollution and impact in European countries are presented below (Table 3, next page).

Table 3. Examples of regulations, standards and guidelines covering odour pollution and impact in the European Union

Country	Regulation/Standard/Guideline	Contents
Austria *(Guidelines to Assess Pollution)*	BMLFUW (2014)	Indoor Odours Guide - Sensory Identification and Evaluation
	BMLFUW (2017)	Directive on Evaluation of Ambient air Concentration of Odours from Livestock
European Union	EN-13725:2003	Air quality-Determination of Odour Concentration by DO
	EN-16841:2016 Part 1 and Part 2	Determination of Odour in Ambient Air by using FI
Germany	VDI 3883:1995 Part 1	Assessment of Odour Annoyance - Questionnaires
	VDI 3883:1993 Part 2	Determination of Annoyance Parameters by Questioning: Repeated Brief Questioning of Neighbour Panellists
	VDI 3883:2014 Part 3	Conflict management in air pollution abatement - Fundamentals and Application to Ambient Odour
	VDI 3883:2017 Part 4	Processing Odour Complaints
	VDI 3940:2010 Part 3	Determination of Odour Intensity and Hedonic Odour Tone
	VDI 3886:2019 Part 1	Odour survey - Determination of Necessity and References for Preparation
	VDI 3788 Part 1	Dispersion of Odorants in the Atmosphere
	Federal Immission Control Act (BImSchG)	It sets limits to odour emissions and technical guidelines for air pollution prevention.
Italy	Deliberazione Giunta Regionale nº IX/301815 -February 2003	Regional regulations for the characterization and mitigation of emissions from odorous-impact activities (Region of Lombardy, Region of Piemonte, Region of Puglia, Province of Trento)
	Deliberazione Giunta Regionale nº1087 – Juny 2016	
	Deliberazione Giunta Regionale nº 13-4554 9 -January 2017	
	Regional Law Puglia 32/2018	
Spain	A draft Against Odorous Pollution (Catalonia)	It is used as a reference to set odour limits from different emitting activities elsewhere in Spain
	Odour Perception Index (Canary Islands)	This municipality has developed an "odour perception index" taking into account odour concentration, hedonic tone, duration of the odour, intermittency and wind direction, among others.
United Kingdom	H4 Odour Management - how to comply with your environmental permit	Guidelines published by Environmental Protection Agencies in UK
	British Institute of Air Quality Management - Guidance on the assessment of odour for planning	
	Odour impact assessment guidance for permitted and licensed sites	

Source: compilation based on information supplied by (103, 139)

Objective

This paper aimed to evaluate the association between residential or occupational short- and long–term exposure to odour pollution from industrial sources and the health status of the exposed population. The association was evaluated by analysing quantitative and qualitative data obtained from the scientific evidence gathered.

This evidence synthesis is based on an objective, transparent, published method that calls for extracting and interpreting data in a systematic manner from multiple domains, including human exposure, epidemiological evidence, mechanistic evidence and biological plausibility. The process involved multiple collaborators (experts on the topic and reviewers) and required an extensive literature search, review, and synthesis of the evidence.

This general objective is addressed by three more specific objectives.

1. To investigate the association between short and long-term exposure to industrial odours and health.
2. To gather all available observational evidence by using a systematic approach to obtain answers to our research question.
3. To combine results (quantitative data) of similar studies through a statistical approach named meta-analysis. To identify a common statistical measure of association that is shared among studies derived from the systematic review and to calculate a weighted average of that common measure.

Methods/Design

Protocol and registration

Methods and inclusion criteria of the systematic review were specified in advance and registered for PROSPERO (registration number: CRD42018117449). The systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (141-143).

Eligibility criteria. Inclusion and exclusion of studies

Eligibility criteria was defined based on the PECO statement for the key elements (population, exposure, comparator and outcome) (144). The population of interest were people of any age living near industrial sources, or workers exposed to odour pollution in their workplace. The definition of an industrial source was limited to all production facilities and processing plants for chemicals, petrochemicals, manufacturing, waste or water disposal and/or treatment, cement, power generation, mining and metals; other activities were also included, such as production in industrial installations of pulp and paper, textile, slaughterhouses and livestock operations (140).

The working party agreed to follow the minimum criterion for inclusion and exclusion of studies hereunder:

- Regarding the eligible exposure and its assessment, studies that captured and measured any environmental odour from industrial activities, assessed by subjective and/or objective measurements, were included. Nevertheless, studies that mainly were focused on emissions of malodorous toxic compounds were excluded due to their difficulties to disentangle the odour effect from the chemical one. Furthermore, studies that assessed the effects of exposure of indoor odour pollution were also excluded.
- Regarding the eligible outcome and its assessment, primary outcomes for which there was a *biological plausibility* with the exposure, such as wheezing and asthma, cough, headache, nausea and vomiting, were considered and included. Odour annoyance was considered both as a surrogate for exposure and outcome, having a strong association with odour intensity, hedonic tone and modelled odour

from dispersion models (8). Secondary outcomes such as respiratory symptoms, stress-related symptoms, other health consequences (e.g., cardiovascular, sleep disorders), were also considered in the study, as well as the novel outcomes (e.g., mood states) (21). There was no prior restriction on the method that was used for outcome measurement. Both objective and subjective outcomes were considered for inclusion. Studies based on comparisons between odour exposure and odour discrimination, and/or hedonic ratings were excluded. Both observational and experimental study designs evaluating short- and long–term effects of odour pollution with an estimate health effect were included.

- Regarding the comparator definition, the comparison group represented any alternative to the exposed group.

Information sources and search

A preliminary search was conducted in bibliographic databases to identify subject terms and free terms relevant to the review question. Furthermore, we developed a search strategy using a combination of Medical Subject Headings (MeSH) terms and free text terms. The strategy was revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules. The search was implemented in October 26-27, 2018, in Medline (via OVID, 1946 to search date) and EMBASE (1947 to search date). After the final set of studies was identified, the list of references that were reported in the selected reports was reviewed by electronic searching, through Scopus (2004 to search date), to identify additional studies. There were no language, date or location restrictions in the search strategy. Grey literature was sought by examining libraries at some universities (University of Valencia, University of Barcelona, University of La Laguna and Pompeu Fabra University), and national/government/NGO reports (41, 89, 93, 102, 103), by looking at cited references of narrative reviews (6, 8, 124, 145-149), and by hand searching to identify further relevant studies. Searches were conducted in English, however, the working party was able to assess reports in other languages, such as Spanish, Italian, French and German. For studies that were not published in any of these languages, we explored options for translation and assessment for inclusion, such as language translators and native speakers of the language. All search results were stored in EndNote. Furthermore, experts and other researchers in the field were contacted in an attempt to identify additional studies that may have been eligible for inclusion in this review. The Ovid search string is presented in table 4.

Table 4. Search strategy (Ovid)

Population	1. (Work* or occupation*or residen* or living or population or populace or public or communit* or municipal* or neighbourhood* or neighbor* or neighbouring or urban or famil* or proximity or vicinity or location* or located or nearby or near or close or closely or surrounding or exposed).tw.)
Exposure	2. ((((Odor* or malodor** or smell* or odour*) adj5 (waste* or incinerator* or production or landfill* or toxic* or emission* or pesticide* or fertilizer* or fume* or biowaste or composting or sewage or agricultur* or biomass* or environment* or farm*or feeding or treatment or rendering or livestock or animal or metal or industrial or petroleum or chemical or manufactur* or disposal or food or municipal or gaseous or organic or pollution)).tw) OR (((Odor* or malodor** or smell* or odour*) adj5 (operation*or factor* or refiner*or foundr* or facility* or plant* or industry* or processing or activity or activities or husbandry or surrounding or compound* or exposure or monitoring)).tw) OR (exp Odorants/))
Human studies only	1 AND 2 NOT (exp animals/ not humans.sh.)

Study selection

The search results were uploaded into a reference management software (EndNote, Clarivate Analytics) to manage the screening and coding process. Following the removal of duplicates, a multistage screening process was performed.

In the first stage, two reviewers (VGF, MDS) screened all titles removing those clearly not relevant with regard to population, exposure, outcomes or study design (e.g., animal studies, studies of virus and bacteria, genomics research and therapies, biochemical assays, letters to the editors). A list of key words was developed in this phase, in order to enable effective screening and removal of records using EndNote (see *Supplementary material; Appendix S1*).

The study selection in this phase was based on:

- That the manuscript dealt with odour pollution in the outdoor environment related to different industrial activities.
- That the odour exposure had no chemical nature.
- That the manuscript analysed and reported the effect of health problems directly related to odour pollution.
- It was a human study.

Additionally, in this stage, the relevant narrative reviews, which aim to provide an important overview of the topic in question, were screened and separated from the rest for further analysis of their content, identified articles and main findings.

In the second stage, two review authors (VGF, MDS) independently screened all the remaining titles and abstracts from the records obtained from the searches. An inclusive approach was taken, and the studies for which we could not ascertain certain key criteria for their inclusion from the abstract were kept for full-text screening. The studies were included as '*necessary for full-text screening*' if their abstracts were not present or available.

In the final screening stage, the full texts of potentially eligible studies were retrieved for evaluation and inclusion by two reviewers (VGF, MDS). Any discrepancies regarding inclusion or exclusion of a particular study between reviewers was resolved through discussion by third reviewer (CA). Reasons for exclusion at the full-text screening stage were documented and presented in an evidence table.

Data collection process and data items

The standard methods of the *Cochrane Handbook for Systematic Review of Interventions* were employed (150). For studies that met inclusion and exclusion criteria, two review authors independently extracted data using a data extraction form. Disagreements about the extracted information were resolved by discussion with the involvement of the research team when necessary. A data extraction sheet was developed on Microsoft Excel©.

Three authors were contacted for further information. All authors responded, one of them provided numerical data that had only been presented graphically in the published article, one provided a digital poster, nevertheless, the remaining author could not provide the requested information.

The reviewers extracted data on study year and design from each study, sampling time frame, region or country where the study was performed, sample size (target, enrolled, follow-up rates) and characteristics of the population, description of the reference or control group, exposure definition (data sources) and assessment (e.g. distance from the facility, odour annoyance using a 5-point-likert scale or dispersion modelling odour assessment), health outcomes collected (methods used to measure the outcome) and missing data, statistical approach performed by the authors to analyse the data, confounders or co-exposures (methods used to measure them and how they were considered in analysis), type of effect measure (Risk Ratio, RR; Prevalence Ratio, PR; Odds Ratio, OR; beta coefficients; absolute and relative change) and the 95% confidence interval (CI).

Regarding data extraction from each study, in cases where more than one effect measure was available from the same report, the following sequential but alternative criteria (if the first does not apply, the second works and so on) were applied to choose estimates to be extracted: those which resulted from the model adjusted for a greater number of confounders (e.g. *Aatamila et al. 2011*, *Hooiveld et al. 2015*); those greatest or most statistically significant among similar categorization for the same exposure (e.g. *Mirabelli et al. 2006*, *Blanes-Vidal 2015*) (13, 19, 29, 151); those with largest effect size. Information on funding and conflict of interest by the authors of the studies was extracted and considered when available.

Risk of bias assessment in individual studies

The risk of bias (RoB) of included studies was independently assessed by two reviewers. Any disagreements were discussed and resolved with a third author by consensus. The National Toxicology Program/Office of Health Assessment and Translation (NTP/OHAT) Risk of Bias Rating Tool for Human and Animal studies adapted to the review question was employed (152, 153). The tool considered nine domains: assessment of exposure, assessment of outcome, confounding (three elements), selection bias, performance bias, attrition/exclusion bias, outcome reporting bias, inappropriate statistical methods, as an additional category for other potential threats to internal validity.

According to the OHAT risk-of-bias tool, for each specific domain, the questions required to choose between a four-point scale: "definitely low", "probably low", "probably high", and "definitely high". Additionally, the OHAT method was used to classify individual studies into an overall quality category, e.g., tiers from 1 (higher quality) to 3 (lower quality). Besides, this approach considers several risk-of-bias domains or key elements of higher relevance based on study design. Key elements for observational studies were *(1) confidence in the exposure characterization, (154) confidence in the outcome assessment and (155) accounting for confounding and modifying variables*.

The assessment of confounding was based on three elements: 1) the design or analysis accounting for confounding and modifying variables, 2) the adjustment for other concurrent exposures 3) the confounding variables measured reliably and consistently. The first two elements were evaluated according to the minimum set of confounders and co-occurring exposures considered *a priori* as relevant by bibliographic search (21, 28, 155, 156) and consensus among all parties involved: sex, age, educational level/ socioeconomic status (SES)/ employment status, smoking status (active/passive) and any co-exposures (noise, traffic pollution, air pollution, indoor odour). An exception was made for the panel studies, which match each case by itself and therefore are able to control by design for individual confounders.

The entire body of evidence was rated and grouped as having "not likely", "serious" or "very serious" RoB, based on the risk of bias across studies and classification tiers. Confidence ratings were integrated on a standard evidence profile table (*Results*, table 6).

Data synthesis

The characteristics and methods of all included studies were provided by creating summary tables (*Results*, table 5). Data patterns were explored and evaluated, and subsequently, a discussion of the study findings was included. The results section was structured by the following outcome groups:

- General ill feelings (e.g., headache, sleeping problems)
- Gastrointestinal symptoms (e.g., nausea/vomiting, reflux)
- Lower and upper respiratory symptoms (e.g., cough/phlegm, wheezing)
- Immune function/allergy mucus irritation
- Skin disorders
- Mood states
- Cardiovascular problems

Where appropriate, the results have been summarised by the type of exposure (objective or subjective) and population of interest (adults, children or workers). For continuous outcomes, mean differences (MDs) and beta coefficients with 95% CI were considered for each study when present. ORs and PRs with 95% CI were considered for dichotomous variables.

The reported outcomes did not necessarily provide effect size in all studies. Some authors occasionally only presented results descriptively. In this sense, where statistical analyses were inappropriate or unfeasible, a discursive account of the results was presented with supporting tables. When it was feasible to combine studies, a random-effects model of meta-analyses was used for each outcome.

From each study, outcome-specific odour-related effects were extracted into evidence tables. For primary outcomes, when at least 3 studies provided effect estimates by comparing exposed subjects versus not exposed, the study-specific estimates of odour-related effect was pooled. Studies assessing the effect using different metric (e.g., beta coefficients for unit increase in odour or risk ratio across multiple exposure categories) were not included due to the heterogeneous methods. Pooled estimates were obtained using random effects models (Restricted Maximum Likelihood REML Method) (157). Heterogeneity was evaluated with the I squared statistic (158), where 25%, 50% and 75% indicate a low, medium, high heterogeneity respectively. To assess if quantitative

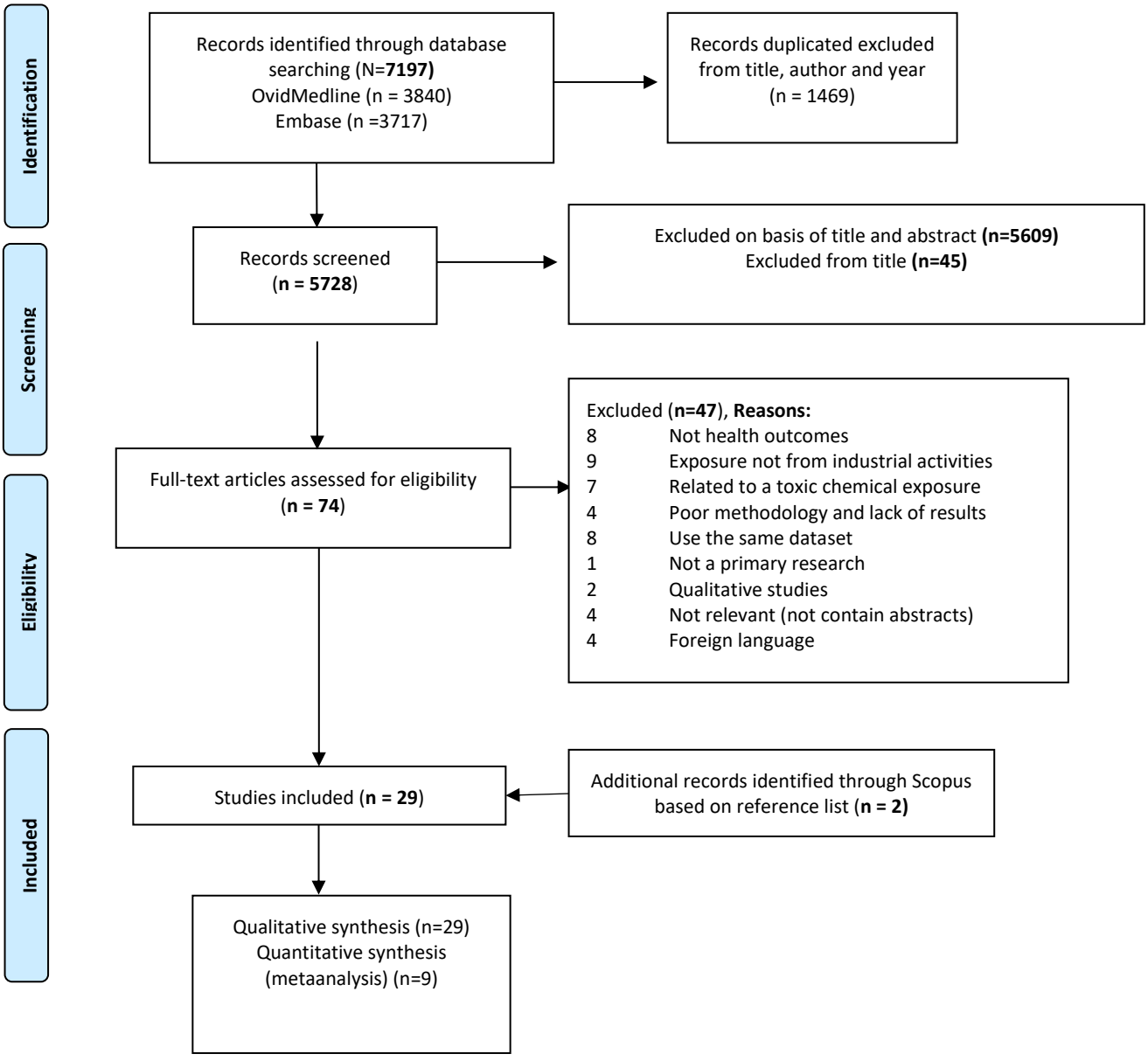
assessment of exposure was a potential explanatory factor for the heterogeneity, a stratified analysis was carried out for studies with objective and subjective exposure assessment. The presence of publication bias was evaluated only for pooled estimates with at least ten effect estimates. The Egger test was used (159), a test for asymmetry of the funnel plot based on the hypothesis that the Y intercept is zero from a linear regression of standardized study-specific effect, ln(OR)/ES(ln(OR)) as dependent variable, and the inverse of standard error 1/ES(ln(OR)) as independent variable.

Data extraction, evidence tables, narrative synthesis and RoB assessment were documented using Microsoft Excel ©. Meta-analyses and forest plots were carried out in STATA software version 14.0.

Results

Figure 11 shows the process of selection of the studies. We identified 5728 records after the removal of duplicates. Of these, 5654 were discarded on the base of title and abstracts in accordance with selection criteria previously described (see *Study selection*).

Figure 11. Flow diagram of the selection process using the PRISMA guidelines



Source: (141)

74 records were subsequently included in the full-text evaluation. 47 references did not meet the inclusion criteria and were excluded with reasons. A full list of these excluded studies, along with reason for exclusion, can be found in appendix S2, characteristics of excluded studies. Lastly, a total of 29 studies were included in the final synthesis including two additional records identified through reference list of the studies. For a further description of the screening process, see the study's flow diagram (Figure 11).

Study characteristics

The characteristics and PECO aspects of included studies are summarized in Table 5.

Table 5. Summary of the PECO aspects of included studies in the systematic review and meta-analysis

Study, Country, Study design	Industrial source	Study population, age group	Exposure assessment	Outcome assessment	Statistical analysis	Adjustment for confounders
Kret 2018 (12) **USA** **Cross-sectional**	Waste (landfill)	N=343 adults' households within a 3.2-km radius (173 exposed; 170 non-exposed)	Distance (km)	Questionnaire: self-reported prevalence of diseases and 12 months symptoms; odour annoyance (5-point Likert scale) **Groups:** Odour nuisances Lower respiratory symptoms Upper respiratory symptoms Gastrointestinal symptoms Mucus irritation General ill feeling	**Model:** n.a **Effect estimated:** n.a Weighted prevalence (95%CI)	Matching for percentage of white population and for 25+ population with education level at least high school. No effect estimate.
Hayes 2017 (22) **Australia** **Cross-sectional**	Wastewater treatment Plant	N=153 residents within a 3-km radius on two exposed (with a history of high or low number of complaints) and one control sites	Distance zones (0-1 km, 1-2 km, 2-3 km) Questionnaire (presence/absence of bad smells and odours impacting community)	Questionnaire: Self-reported psychological symptoms past week; odour annoyance (10-point scale) **Groups:** Mood states	**Model:** ANOVA **Effect estimated**: None	Social readjustment scale by Holmes and Rahe 1967(Holmes and Rahe 1967) added as covariate
Tjalvin 2015 (37) **Norway** **cross-sectional**	Chemical Industry (Chemical explosion in an Industrial harbour)	N=284 workers in 2008 and 203 in 2012 (exposed workers employed in 2008 and/or clean-up workers, proximity to the explosion ≤ 1 km; control workers) range of age 18-67	Questionnaire: Worker's exposure history	Subjective Health Complaints (SHC) score **Groups:** General ill feeling Gastrointestinal symptoms Upper respiratory symptoms Immune function Cardiovascular problems	**Model:** Linear mixed effects models with random intercept and slope **Effect estimated:** Mean difference	Age, gender, smoking habits, educational level.
Tjalvin 2017 (160) **Norway** **cross-sectional (repeated survey of Tjalvin 2015)**	Chemical Industry (Chemical explosion in an Industrial harbour)	N=486 workers employed in 2008 (18% present during the explosion), in 2010 (n=379), 2012 (n=252) Adults aged 18-67 years	Questionnaire: Low/high odour score (% of months each participant noticed the odour in 2008)	Questionnaire: Subjective Health Complaints (SHC) score previous month; Impact of Event Scale-Revised (IES-R) previous 7 days **Groups:** General ill feeling Mood states	**Model:** Linear mixed effects models with random intercept and slope **Effect estimated:** Mean difference	Age, gender, smoking habits, educational level, absence/presence during the explosion (> 1 km or ≤ 1 km)

Table 5. Summary of the PECO aspects of included studies in the systematic review and meta-analysis, Continued

Study, Country, Study design	Industrial source	Study population, age group	Exposure assessment	Outcome assessment	Statistical analysis	Adjustment for confounders
Hooiveld 2015 (19) **Netherlands** **Cross-sectional**	Animal feeding operations	N=753 adults, residents with asthma or lower back pain	Questionnaire: Self-reported odour annoyance (yes/no)	Questionnaire: Self-reported symptoms last month; general health (5-point Likert scale from bad to very good) **Groups:** Gastrointestinal symptoms General ill feelings Lower respiratory symptoms Upper respiratory symptoms Mood states	**Model:** Multiple ordinal logistic, logistic and Poisson regression analysis **Effect estimated:** ORs(95%CI)	Smoking status, growing up at farm, age, gender, nationality, marital status, educational level, asthma or lower back pain, other environmental annoyances (noise, traffic and air pollution)
Boers 2016 (28) **Netherlands** **Cross-sectional**	Animal feeding operations	N=582 residents living near livestock farms Mean age=51 years old (SD 13) (part of the population included in Hooiveld 2015)	Calculated exposure: 98th percentile of odour concentrations (OU_E/m^3) from Stacks dispersion model	Questionnaire: Self-reported odour annoyance (4-point scale) **Groups:** Odour nuisances	**Model:** multivariate logistic regression analysis Effect estimated: ORs(95%CI)	Age, educational level, indoor air pollution, asthma, or lower back pain
Baldacci 2015 (35) **Italy** **Cross-sectional**	Waste (incinerator)	N=1407 residents within 4-km radius from the incinerator and a control group. Mean age 44.4 (SD 22.1)	Questionnaire: Self-reported odour annoyance (no, slightly annoying, very annoying)	Questionnaire: Self-reported symptoms past 12 months. **Groups:** Lower respiratory symptoms Upper respiratory symptoms	**Model**: Multivariate logistic regression analysis **Effect estimated:** ORs(95%CI)	Gender, age, residence/incinerator distance, educational level, working position, smoking status, passive smoking, residential time, and occupational exposure.
Blanes-Vidal 2015 (13) **Denmark** **Cross-sectional**	Waste (biodegradable)	N=454 Residents from six study areas in Denmark. Mean age 54 (SD 14)	NH_3 concentration: log_e (NH^3 exposure), NH_3 exposure levels (<2, 2-3, > 3 ug/m^3), Questionnaire: Self-reported odour annoyance (no, slightly, moderately, very, extremely)	Questionnaire: Self-reported symptoms past 2 years, odour annoyance ((no, slightly, moderately, very, extremely) **Groups:** Odour nuisances Gastrointestinal symptoms General ill feeling Mood states	**Model:** multivariate logistic regression analysis **Effect estimated:** ORs(95%CI)	Age, gender, smoking habit, job, time spent at home per week, existence of household residents below 18 years old, years living in the region, and acute and chronic respiratory conditions

Table 5. Summary of the PECO aspects of included studies in the systematic review and meta-analysis, Continued

Study, Country, Study design	Industrial source	Study population, age group	Exposure assessment	Outcome assessment	Statistical analysis	Adjustment for confounders
Wing 2014 (161) **USA** **Cross-sectional**	Sewage Sludge and Animal feeding operations	N=158 adults, residents living near liquid TSS, 85 living near cake TSS, and 188 living in comparison areas	Questionnaire: Self-reported odour annoyance past six months (none/faint and moderate/strong/very strong)	Questionnaire: Self-reported symptoms past six months **Groups:** Gastrointestinal symptoms Mucus irritation General ill feeling Lower respiratory symptoms Upper respiratory symptoms Skin disorders	**Model:** Linear and poisson regression analysis **Effect estimated:** Mean factor score differences (95%CI) and PRs (95%CI)	Age, gender, race, educational level, smoking status, passive smoking, agricultural chemical odours and odours from burning
Wing 2013 (162) **USA** **Panel (2 weeks)**	Animal feeding operations	N=101 non-smoking residents living within 1.5 miles of an CAFOs source Adults aged ≧18 years old. Mean age 53.7 (19.2-89.5)	Data-collection diary: Self-reported odour annoyance (9-point Likert scale)	Systolic (SBP) and diastolic (DBP) blood pressure values **Groups:** Cardiovascular problems	**Model:** Linear fixed-effects models **Effect estimated:** β (SE)	Time-of-day (AM or PM)
Aatamila 2011 (29) **Finland** **Cross-sectional**	Waste (Landfills and composting sites)	N=1142 residents within a 5-km radius of six different biowaste sites Range of age: 25-64 years	Distance zones (<1.5, 1.5-3, >3 km) Questionnaire: odour perception (4-point scale) stratified into sensitive vs not sensitive, odour annoyance (4-point scale) categorized as annoyed vs not annoyed	Questionnaire: Self-reported symptoms past 12 months **Groups:** Gastrointestinal symptoms Mucus irritation General ill feeling Lower and upper respiratory symptoms Skin disorders	**Model:** Logistic regression analysis **Effect estimated:** ORs(95%CI)	Model 1: adjusted for sex, age, educational level, SES, and smoking Model 2: additionally, adjusted for odour sensitivity
Heaney 2011 (34) **USA** **Panel (14 days)**	Waste (landfill)	N=23 adults, residents within 0.75 miles of the landfill	Questionnaire: 12-hr of self-reported odour annoyance (5-point Likert scale)	Questionnaire: Self-reported symptoms past 12-hr **Groups:** Gastrointestinal symptoms Mucus irritation	**Model:** Conditional fixed effects logistic regression models **Effect estimated:** ORs(95%CI)	Time of day (AM/PM)

Table 5. Summary of the PECO aspects of included studies in the systematic review and meta-analysis, Continued

Study, Country, Study design	Industrial source	Study population, age group	Exposure assessment	Outcome assessment	Statistical analysis	Adjustment for confounders
				General ill feeling Lower respiratory symptoms Upper respiratory symptoms Mood states Skin disorders		
Schinasi 2011 (163) **USA** **Panel (14 days)**	Animal feeding operations	N=101 Non-smoking residents within 1.5 miles of an AFOs source Mean age 53.7 (19.2-89.5)	Questionnaire: 12-hr of self-reported odour annoyance (9-point scale)	Questionnaire: Self-reported symptoms past 12-hr Clinical measurements: Lung function (forced expiratory volume or $FEV_1$and peak expiratory flow rate or PEF) **Groups:** Gastrointestinal symptoms Mucus irritation General ill feeling Lower respiratory symptoms Upper respiratory symptoms Skin disorders	**Model:** Conditional fixed effects logistic and linear regression analysis **Effect estimated:** β (SE)	Time of day (AM/PM)
Herr 2009 (7) **Germany** **Cross-sectional**	Waste (composting sites)	N=477 residents living "near" two composting sites. (263 EnvExp2 and 214-control group). Individuals aged ≧16 years old	Distance (km): EnvExp2 (odour-only exposed) and a control group	Questionnaire: Self-reported symptoms past 2 years **Groups:** Gastrointestinal symptoms General ill feeling Lower respiratory symptoms Mood states Skin disorders Cardiovascular symptoms	**Model:** Logistic regression analysis **Effect estimated:** ORs(95%CI)	Adjusted for age, gender, and educational level
Horton 2009 (164) **USA**	Animal feeding operations	N=101 Non-smoking residents within 1.5 miles of an AFOs source	12-hr of self-reported odour annoyance (9-point scale)	Questionnaire: Self-reported information on mood states **Groups:** Mood states	**Model:** Logistic mixed models with random intercepts. **Effect estimated:** β	Time of day (AM/PM)

Table 5. Summary of the PECO aspects of included studies in the systematic review and meta-analysis, Continued

Study, Country, Study design	Industrial source	Study population, age group	Exposure assessment	Outcome assessment	Statistical analysis	Adjustment for confounders
Panel (2 weeks)		Mean age 53.7 (19.2-89.5)		Odour nuisances	(SE) and ORs(95%CI)	
Sucker 2008 (16) **Germany** **Cross-sectional**	Industrial sites	N=1434 adults from each household (the homemaking or the person spending most of the time at home)	Questionnaire: Log-values of odour frequency Intensity (6-point scale from "very slight" to "extremely strong"), Hedonic tone (9-point scale with values ranging from "-4" "extremely unpleasant" through "0" "neither pleasant nor unpleasant" to "+4" "extremely pleasant")	Questionnaire: Odour annoyance; self-reported health complaints **Groups:** Odour nuisances General ill feeling Mucus irritation	**Model:** Logistic regression analysis. **Effect estimated:** ORs(95%CI)	Noise disturbance, length of residence, quality of residential area, tenant or owner, single/multiple houses, average time at home, perceived health, smoking habit, gender, age, marital status, educational level
Radon 2007(165) **Germany** **Cross-sectional**	Animal feeding operations	N=5556 Residents from four rural town with high density of AFOs Mean age 33.6 (SD 7.4)	Questionnaire: Self-reported odour annoyance (4-point Likert scale from "not at all" to "strongly")	Questionnaire: Self-reported symptoms during the week. Clinical measurements: Specific IgE to common allergens >0.35 IU/mL, bronchial hyperresponsiveness to methacholine, forced expiratory volume in 1 second (FEV_1) **Groups:** Lower and upper respiratory symptoms Immune function and allergy	**Model:** Logistic and linear regression analysis **Effect estimated:** ORs(95%CI)	Age, sex, active and passive smoking, educational level, number of siblings and parental allergies. FEV_1 additionally, adjusted for passive smoking during childhood
Mirabelli 2006 (151) **USA** **Cross-sectional**	Animal feeding operations	N=58169 students of 265 schools within 3 miles of at least one AFO source Range of age: aged 12-14	Distance (miles) from nearest swine AFO (<3, ≥3) Questionnaire: self-reported indoor and outdoor odours from schools (binary coded	Questionnaire: Current and past 12-month self-reported respiratory symptoms and medical care **Groups:** Lower respiratory symptoms General ill feeling	**Model:** Random-intercepts binary regression analysis **Effect estimated:** PRs (95%CI)	Age, race, socioeconomic status, smoking, school exposures and household exposures

Table 5. Summary of the PECO aspects of included studies in the systematic review and meta-analysis, Continued

Study, Country, Study design	Industrial source	Study population, age group	Exposure assessment	Outcome assessment	Statistical analysis	Adjustment for confounders
			variable, "reported"/"no reported")			
Avery 2004 (15) **USA** **Panel (2 weeks)**	Animal feeding operations	N=15 residents within 2.4 km of an intensive hog operation facility Mean age 55.3 (SD 13.4).	Questionnaire: Self-reported odour annoyance (9-point scale, coded as a seven-level continuous variable)	Clinical measurements: Log salivary IgA concentration (μg/ml) and secretion rate (μg/ml) **Group:** Immune function and allergy	**Model**: Hierarchical mixed models **Effect estimated:** β (SE)	Day of data collection (1-14) and time of day (AM/PM)
Radon 2004 (58) **Germany** **Cross-sectional**	Animal feeding operations	N=2745 Residents living in rural towns close to intensive animal production Mean age 32.7 (SD 7.7)	Questionnaire: Self-reported odour annoyance (4-point Likert scale from "not at all" to "extremely")	QoL questionnaire: Physical SF-12 score, emotional SF-12 score **Groups:** General ill feeling Mood states	**Model:** Multiple linear regression analysis **Effect estimated:** β (SE)	Age, gender, respiratory symptoms, smoking, living on or close to a farm and employment status.
Segala 2003 (18) **Canada** **Cross-sectional**	Wastewater treatment plant	N=2867 residents from 8 nearby towns. Distance zones: 3-4.5 km (N=1003), mean age 47.5 (S.D. 15.2) 1.5-3 km (N=1007), mean age 48.2 (S.D. 67.7) < 1.5km (N=857), mean age 49.8 (S.D 15.1)	Distance zones (<1.5, 1.5-3, 3-4.5 km) Questionnaire: Self-reported odour tolerance ("tolerant", "moderately tolerant", "intolerant"), odour annoyance ("annoyed with impact on health", "annoyed without impact on health", "not annoyed")	Questionnaire: Self-reported symptoms past month and year **Groups:** Gastrointestinal symptoms Mucus irritation Lower respiratory symptoms Upper respiratory symptoms General ill feeling Cardiovascular problems	**Model:** Multivariate logistic regression analysis **Effect estimated:** ORs(95%CI)	Age, sex, educational level, active vs inactive, smoking status, family size, satisfaction with neighbourhood life
Georgieff, 1999 (166) **Bulgaria** **Cross-sectional**	Paper industry	N=538 Residents from Stamboliyski town Range of age: 16-60 years old	Questionnaire: Self-reported unpleasant odour (yes/no)	Questionnaire: Self-reported symptoms **Groups:** General ill feeling Lower respiratory symptoms Mood states Immune function and allergy	**Model:** n.a. **Effect estimated:** n.a. Percentages (%) of number of reported somatic symptoms	None

Table 5. Summary of the PECO aspects of included studies in the systematic review and meta-analysis, Continued

Study, Country, Study design	Industrial source	Study population, age group	Exposure assessment	Outcome assessment	Statistical analysis	Adjustment for confounders
Steinheider 1998 (31) **Germany** **Cross-sectional**	**Nettetal study** Fertilisers production plant **Nörvenich study** Pig rearing facilty	**Nettetal study (**N= 250) **Nörvenich study (**N= 322) Adults aged ≧18 years old	**Nettetal study** 1) Distance from the odour source Close: within 400-800 m Medium: 1600 m Far (control area): 6 and 3.5 km 2) 11-point graphic scale of Odour annoyance **Nörvenich study** 1) Log-values of odour frequency (odour hours/year). 34 observation points; 2) 11-point graphic scale of Odour annoyance	Questionnaire: Self-reported symptoms and odour annoyance (11-point graphic scale) Control variables (fever and asthma attacks) **Groups:** Odour nuisances Gastrointestinal symptoms General ill feeling Lower respiratory symptoms Mood states	**Nettetal study** **Model:** Analysis of variance **Effect estimated:** None **Nörvenich study** **Model:** Linear regression analysis. **Effect estimated:** β (SE)	None
Schiffman, 1995 (167) **USA** **Panel (4 days)**	Animal feeding operations	N=88 Exposure group: Mean age 52.0 ± 13.4 Control group: Mean age 51.7 ± 8.3	Distance and duration: Exposed living an average of 5.3 + 6.5 years near hog operations and comparison group	Profile of Mood States (POMS) factors and Total Mood Disturbance (TMD) score **Groups:** Mood states	**Model:** ANOVA **Effect estimated:** n.a.	adjusted by design (matching by gender, age, race and education)
Steinheider 1993 (168) **Germany** **Cross-sectional**	Industrial sites 1) Duisburg-chemical plant 2) Dortmund – iron/steel plant 3) Brühl – castiron factory and sugar refinery	N=1539 adults, living near of four cities in North Rhine-Westphalia. **Duisburg** (N=400**),** **Dortmund** (N=400), **Brüh**l (N=539), **Rodenkirchen** (N=200)	Log-values of odour frequency (odour hours/year).	Questionnaire: Self-reported odour annoyance (11-point scale) **Groups:** Odour nuisances	**Model:** Multivariate linear regression analysis **Effect estimated:** n.a.	Age, sex, educational level, profession, length of residence and perceived health. Dortmund, Brühl and Rodenkirchen added coping strategies to the model

Table 5. Summary of the PECO aspects of included studies in the systematic review and meta-analysis, Continued

Study, Country, Study design	Industrial source	Study population, age group	Exposure assessment	Outcome assessment	Statistical analysis	Adjustment for confounders
	4) Rodenkirchen – oil refineries					
Lipscomb 1991 (169) **USA** **Cross-sectional**	Waste (McColl waste disposal site)	N=193 residents living nearby a disposal waste site Adults ≧22 years old	Exposure areas (high, medium, and low) based on an odour survey conducted in 1981 (170)	Questionnaire: Self-reported symptoms past 12 months **Groups:** Odour nuisances Gastrointestinal symptoms Mucus irritation General ill feeling Lower respiratory symptoms Upper respiratory symptoms Mood states Skin disorders Immune function and allergy	**Model:** n.a. **Effect estimated:** Crude PORs(95%CI)	None
Shusterman 1991 (20) **USA** **Cross-sectional**	Waste	N=2040 residents living near three hazardous waste sites in Southern California McColl. Acid petroleum sludge (N= 670) Operating Industries. Municipal and sewage (N= 514) Del Amo-Montrose. Residues from synthetic rubber manufacturing (N= 856)	Self-reported frequency of odour perception ("none", "less than or equal to four times per month" and "greater than four times per month"	Questionnaire: Self-reported symptoms **Groups:** Odour nuisances Gastrointestinal symptoms Mucus irritation General ill feeling	**Model:** n.a. **Effect estimated:** PORs(95%CI)	None
Deane 1977 (171) **USA** **Cross-sectional**	Paper industry	N=140 Adults living in three residential areas nearby a pulp mill	Exposure areas: high (1-2 miles southeast of the mills), moderate (2-3 miles east of the mils), low (4 miles east of the mills)	Questionnaire: Self-reported symptoms **Groups:** Odour nuisances Gastrointestinal symptoms	**Model:** n.a. **Effect estimated:** Frequency of self-reporting outcomes	Analysis were stratified by odour annoyance and gender

Table 5. Summary of the PECO aspects of included studies in the systematic review and meta-analysis, Continued

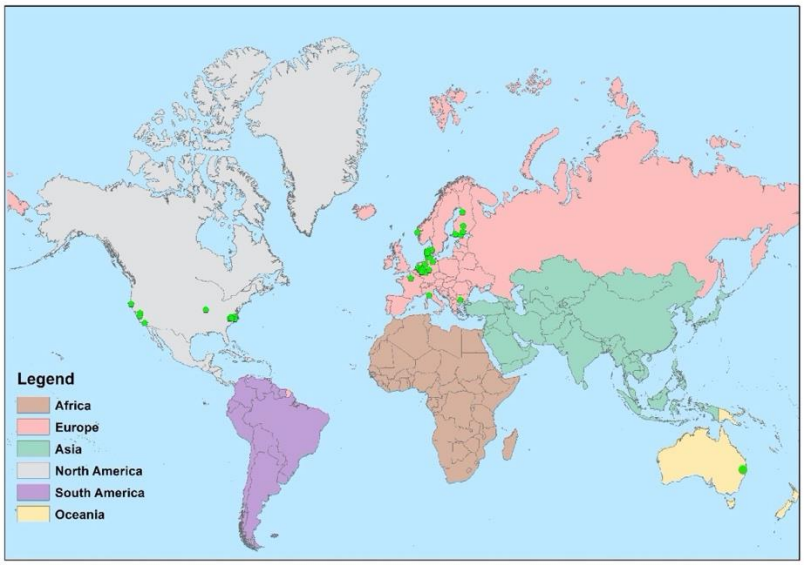
Study, Country, Study design	Industrial source	Study population, age group	Exposure assessment	Outcome assessment	Statistical analysis	Adjustment for confounders
				Mucus irritation General ill feeling Lower respiratory symptoms Upper respiratory symptoms Mood states		
Deane, 1978 (36) **USA** **Cross-sectional**	Refineries and other petrochemical industries	N=291 Residents living in three residential areas nearby refineries and petrochemical plants	Exposure areas estimated by dynamic olfactometry: High (Area I), Moderate (Area II), Low (Area III).	Questionnaire: Self-reported symptoms **Groups:** Odour nuisances Gastrointestinal symptoms Mucus irritation General ill feeling Lower respiratory symptoms Upper respiratory symptoms Mood states	**Model:** n.a. **Effect estimated:** n.a. Frequency of self-reporting outcomes	None

n.a. not applicable

SES socioeconomic level

Figure 12 shows the geographical distribution of the studies by country, mostly in Europe (see *Supplementary material; Appendix S3 and S4*). The majority of the studies had a cross-sectional design (n=23), whilst six were panel studies (15, 34, 162-164, 167). Studies sizes ranged from 15 to 58.169. Mixed populations of adult males and females comprised the study population for most included studies. Only one study, *Mirabelli et al.*, involved a sample of school-age children (age range: 12-14 years)(151).

Figure 12. Geographic distribution of the selected studies



The collected information showed the heterogeneity in terms of type of industrial source, study population, measurements for exposure and outcome (e.g., objective or subjective) and type of outcomes. Regarding industrial source of exposure, 12 studies were conducted on AFOs (15, 19, 28, 31, 151, 161-165, 167, 172), 10 studies on waste (both solid and liquid waste) (7, 12, 13, 18, 20, 22, 29, 35, 169), 2 were on multiple sites (16, 168), and 6 were on other industrial exposure (e.g., paper, petrochemical plant) (31, 36, 37, 160, 166, 171).

Thirteen studies used objective measurements for exposure (7, 12, 13, 18, 22, 28, 29, 31, 36, 151, 167, 169, 171). Distance to the odorous source was assessed in ten studies (7, 12, 18, 22, 29, 31, 36, 151, 167, 171). *Boers et al.* estimated odour exposure using the *Stacks* dispersion model (28). *Lipscomb et al.* defined a measure of exposure based on odour zones adopted from an earlier survey (169). In addition, *Blanes-Vidal 2015* included NH_3 exposure as a proxy of

odour exposure; *Blanes-Vidal et al. 2012* previously suggested in another investigation that NH_3 exposure could be used as a predictor of odour annoyance (13, 33). In one study, two different exposure measures were used, distance and odour frequency measured by a group of trained panellists (31). In a previous study by the same authors, well-trained panellists measured frequency of odour observations that were transformed into percent odour hours (173). In 15 studies (13, 15, 16, 18-20, 31, 34, 161-165, 168, 172), the perceived level of exposure was rated labelling different scales (Likert-type scales and other alternatives) through questionnaires/interviews. Several studies used a dichotomous exposure of odour annoyance and/or odour perception, defined as the presence or the absence of it (16, 18-20, 29, 34, 35, 151).

Questionnaire-based retrospective and self-reported information on outcomes was the most widely used method for measuring primary outcomes. Most studies were related to both acute (e.g., symptoms, worsening of disease) and chronic outcomes (e.g., prevalence of diseases). The outcomes had different timings of data collection, with past year prevalence in some studies (12, 18, 29, 35, 151, 169) or past 2 years (7, 13), or past 6 months prevalence (161), past one month (19, 37, 160) or current symptoms (18, 20, 22, 28, 31, 151, 165). On the contrary, the six panel studies focused on short-term or acute outcomes, that varied on a daily base, such as symptoms of disease (34, 163), or mood states (164, 167) or biological parameters lung/bronchial function (163), immune function and allergy (15), blood pressure (162). In addition, a cross-sectional study (165) reported objective outcomes (bronchial hyperresponsiveness to methacholine, IgE concentration) as well. In some studies, information on timing of outcome data collection was not provided (20, 31, 36, 166, 168, 171).

Most cross-sectional studies took into account the following adjustment for confounders: age, sex, smoking status, educational level and/or SES (13, 16, 18, 19, 29, 35, 37, 151, 160, 161, 165, 172). Panel studies (15, 34, 162-164, 167) were adjusted only by time-varying variables (e.g. time of the day when outcome was measured) because they do not need to adjust for individual confounders, since the study population serves as its own control. Eight studies (12, 20, 31, 36, 166, 167, 169, 171) did not account for any confounder, and only one (12) reported to have matched exposed and control population by age, race and education level.

Risk of bias within studies

Table 6 shows the results of evaluation of the risk of bias of the studies selected for the review. The last column includes the tiering evaluation for each study.

Table 6. 1st Tier, 2nd Tier and 3rd Tier according to the NTP/OHAT tiered approach risk of bias tool approach

* Short communications

Overall, the body of evidence was affected by a definitely high risk of bias in exposure and outcome assessment, since most studies used self-reported information. 16 studies were classified in the worst quality level (3rd tier), 9 studies in the second (2nd tier) and 5 studies in the first category (1st tier).

Confidence in exposure and outcome assessment was very low in most studies. Only three studies were judged at low risk of bias since they used objective outcome measures, or only exposure from dispersion models (15, 28, 162). Another critical issue was the lack of control for other exposure (e.g., air pollution).

As for confounding, adjustment with a minimum set of potential confounders was achieved in most studies for which the risk of bias was labelled 'low'. However, eleven studies, which did not account for any confounders, were graded as "probably high" or "definitely high" risk of bias (7, 20, 22, 28, 31, 36, 166, 168, 169, 171). The second confounding element referred to the adjustment of other environmental exposure and, in this case, most studies did not adjust for concurrent exposures. Panel studies usually include the within-subject associations between exposure and outcome. In this sense, panel studies that only accounted for time of day (morning /evening) were considered as "probably high RoB" (15, 34, 162-164), due to the lack of adjustment for time-varying co-exposures, such as air pollution or noise. The third confounding element regarding validity and reliability of measures was characterized by a high risk of bias in most studies, since information was mostly self-reported, such as questionnaire-based data. In some cases, self-reported information was collected by fully trained interviewers who carried out face-to-face interviews or telephoned the subjects (16, 29), nevertheless, we graded them as "definitely high" RoB as well. Eight studies accounted for potential co-exposures, such as smoking, indoor and/or outdoor pollution (7, 16, 19, 34, 151, 161, 163, 164), and they were considered as "definitely low" or "probably low" RoB. Three studies (12, 28, 37) were classified as "probably high" RoB, but only one (12) did not provide sufficient information to be assessed.

The risk of selection bias resulted to be "definitely high" in five studies (16, 22, 161, 166, 169), since the control group could not be considered unexposed. The risk of selection bias was "probably high" in most studies. Addionally in eight studies (19, 28, 31, 37, 151, 160, 172) the RoB was graded as "not reported or NR", due to the fact that no information was provided as

to whether selection of study participants resulted in appropriate comparison groups (table 6). Pairing the cases to themselves, namely, conducting the case-crossover/panel studies minimizes the potential source of selection bias, as the cases are their own-self-matched controls (174). Regarding attrition bias, in twelve studies (7, 18, 31, 35, 37, 160, 164, 166-169), the information provided about loss of participants was unclear or incomplete, so consequently they were considered as "probably high" risk of attrition bias. Higher rates of participation related to exposure history, distance to the source of odour, social factors, such as sex, age or socioeconomic level limit the interpretation and generalisability of the recruited study population (19, 175). Missing values related to outcome variables in the study were treated in the analysis. Only three studies were classified at "definitely low risk" of attrition bias (15, 29, 162). The risk for the outcome reporting bias was judged, when no study protocol was available, by comparing methods and results sections. Five studies were judged at "probably high" or "definitely high" risk of reporting bias (7, 12, 22, 29, 167) and, additionally, two studies, *Georgieff et al.* and *Baldacci et al*. (35, 166), were at unclear risk since the outcomes were not reported with sufficient detail, most likely because they represented short communications. A probably low risk of reporting bias was found in Sucker et al (16), after evaluating a previous publication of another part of the results (17).

Regarding the additional element of appropriate statistical methods, which was further considered, eleven studies were judged at high risk (probably or definitely) since they only provided a descriptive analysis (20, 22, 31, 36, 165-167, 169, 171, 172).

Synthesis of results

Health effects of industrial odours

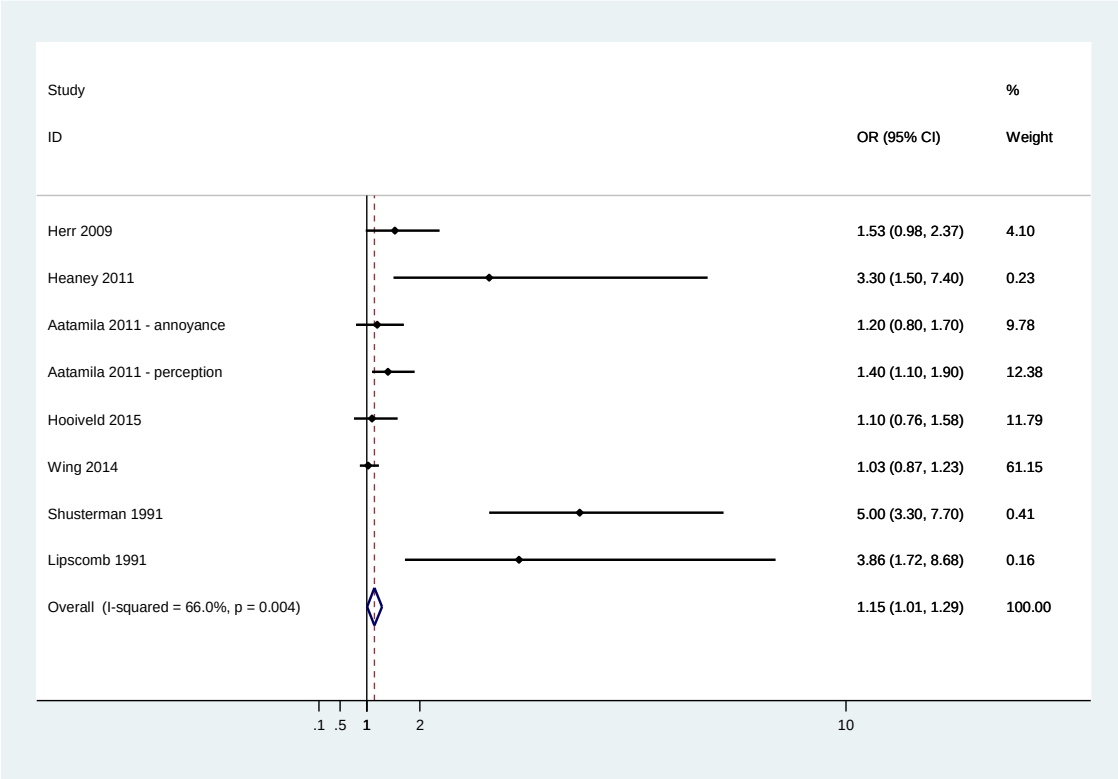
Health outcomes were grouped as follows: general ill feelings (e.g., headache, sleeping problems), gastrointestinal symptoms (e.g., nausea/vomiting, reflux), lower and upper respiratory symptoms (e.g., cough/phlegm, wheezing), immune function/allergy mucus irritation, skin disorders, mood states, cardiovascular problems, and odour nuisances (e.g., odour annoyance, risk perception). We ran meta-analyses for headache, nausea/vomiting and cough/phlegm. Appendices include results, which were not included in the meta-analyses, of the association between residential, or occupational, short- and long–term exposure to odour pollution from industrial sources and the risk associated to it. No measure of association was available for five studies (12, 20, 36, 166, 171) and for one of the locations (*Nettetal*) studied in *Steinheider et al.* (31).

General ill symptoms

19 studies analysed general ill symptoms as health outcome of odour related effects (7, 12, 13, 16, 18-20, 29, 31, 34, 36, 37, 160, 161, 163, 166, 169, 171, 172). All studies were on adults. Two studies were conducted among workers (37, 160).

Headache was the most common general ill symptom, being reported in 16 studies, 7 of which were included in the meta-analysis. When the data were combined, an increased risk of headache in exposed versus not exposed was observed (n=7; OR=1.15, 95% CI: 1.01-1.29) with moderate heterogeneity (I^2 = 66%, p-value = 0.004) (Figure 13). There was no evidence of small-study effects (Egger's test, p-value = 0.108). No study on workers was included in the meta-analysis. No analysis of subgroups was done due to the low number of studies (one with objective exposure and six with subjective exposure).

Figure 13. Forest plot of study-specific and pooled Odds Ratio (OR) and 95% Confidence Intervals (95%CI) of residential exposure to odour and headache in exposed versus non-exposed subjects.



Among studies that were not included in the meta-analysis (see *Supplementary material; Appendix S5*), one study showed increasing headache prevalence (31) and two studies (13, 18) showed increasing risk in the highest exposure categories: at extremely annoyed compared to those who were not annoyed (OR = 3.65; 95% CI: 1.27-10.5); odour intolerant vs tolerant (OR = 2.64; 95% CI 2-3.5); group with complaints with impacts on health vs no complaint group (OR = 2.04; 95% CI 1.46-2.84).

Ten studies evaluated exposure to odour objectively (7, 12, 13, 18, 29, 31, 36, 37, 169, 171), reporting sparse evidence of association for dizziness (7), sleeping difficulties (31), fatigue (169), joint pain (29), fever past 12 months (29) and toothache (169) (see *Supplementary material; Appendices S6, S7, S8, S9, S10*).

Several studies evaluated exposure subjectively (13, 18-20, 29, 34, 161, 163, 171). Most consistent associations were found for dizziness (13, 18, 19, 34), unnatural fatigue (13, 18, 29) and joint/muscular pain (18, 29) (see *Supplementary material; Appendices S6, S8, S9*).

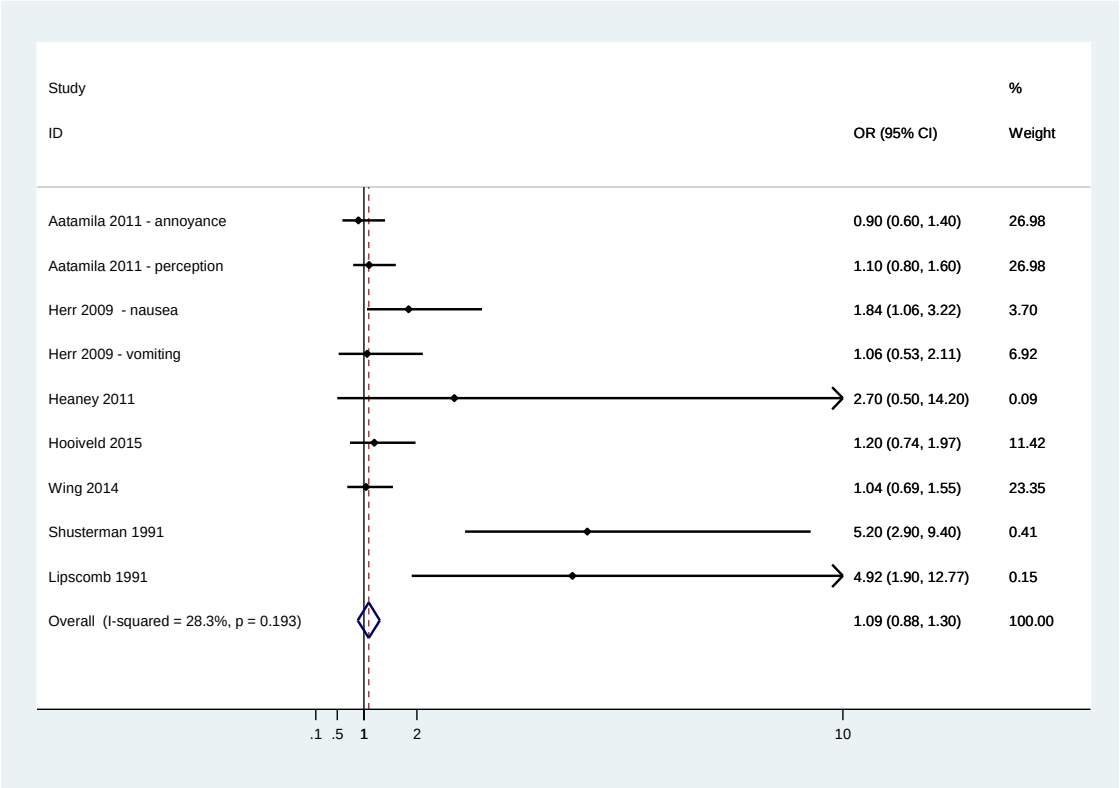
Among exposed workers, significant changes in mean differences in the total subjective health complaint (SHC) score and in the subjective neurological complaints score were found, with a higher score in exposed workers versus in controls; these associations lasted for at least three years after the pollution was removed (37, 160) (see *Supplementary material; Appendix S10*).

Gastrointestinal symptoms

A total of 15 studies reported gastrointestinal symptoms (7, 12, 13, 18-20, 29, 31, 34, 36, 37, 161, 163, 169, 171). All studies were on adults. Only one study included workers (37). The most frequently reported gastric symptom was nausea and vomiting. Only 7 studies (7, 19, 20, 29, 34, 161, 169), providing 10 effect estimates, were feasible to meta-analyse (see figure 14), showing an increased risk of these symptoms (n=7; OR=1.09; 95% CI: 0.88-1.30) with a low heterogeneity (I^2 = 28.3%; p-value=0.193). There was some evidence of publication bias (Egger's test, p-value = 0.042), although power of test was low due to the low number of studies. No analysis of subgroups was done due to the low number of studies (one study with subjective exposure and six studies with objective exposure).

Among studies that were not included in the meta-analysis (see *Supplementary material; Appendix S11*), self-reporting of vomiting, nausea or retching was significantly higher for each increase in odour frequency in Nörvenich site (31), and in the study of *Segala et al*. (18) in the highest exposure categories: odour intolerant vs tolerant (OR = 3.52; 95% CI 2.14-5.8) and in group with complaints with impacts on health vs no complaint group (OR = 2.11; 95% CI 1.13-3.94). Estimates of the odour-nausea association tended to increase as the level of odour annoyance increases, but the results were not significant in *Blanes-Vidal* (13).

Figure 14. Forest plot of study-specific and pooled Odds Ratio (OR) and 95% Confidence Intervals (95%CI) of residential exposure to odour and nausea/vomiting in exposed versus non-exposed subjects.



Among other gastric symptoms, 8 studies measured exposure objectively (7, 18, 29, 31, 36, 37, 169, 171). High exposure to odours was associated with greater prevalence of loss appetite (OR = 4.27; 95% CI: 1.43-12.73) (169). One study (31) showed a higher frequency of gastric symptoms (disgust, loss of appetite, stomach discomfort) when the frequency of odour exposure was increased. Another study (171) reported a significant trend by area among women who had reported frequent or occasional constipation (see *Supplementary material; Appendices S12, S13, S14, S15, S16*).

7 studies evaluated exposure subjectively (18, 19, 29, 34, 161, 163, 171). In this sense, estimates of the odour-nausea association tended to be positive, more likely to experience increased frequency with the level of odour annoyance, but results were fairly imprecise (13). *Segala et al.* (18) reported more frequent diarrhoea in people with self-reported odour intolerance (OR = 2.18, 95% CI: 1.43-3.33) or experienced malodour-related health complaints (OR = 2.83, 95%

CI: 1.82-4.4); however, the same study did not report any significant association in people with complaints not related to health (OR = 1.08, 95% CI: 0.74–1.58). *Aatamila et al.* (29) found an increased risk of diarrhoea in the group with odour perception (OR = 1.3, 95% CI: 1-1.7) and with odour annoyance (OR = 1.2, 95% CI: 0.9-1.7). Statistically significant associations with stomach pain, gastrointestinal symptoms and constipation were reported in *Hooiveld et al*. (19) For other gastrointestinal outcomes associated with odour annoyance, such as loss of appetite, abdominal pain, stomach discomfort or reflux, no conclusive results can be drawn due to the limited number of studies and imprecision of the effect sizes (19, 161, 163) (see *Supplementary material; Appendices S12, S13, S14, S15, S16, S17*)).

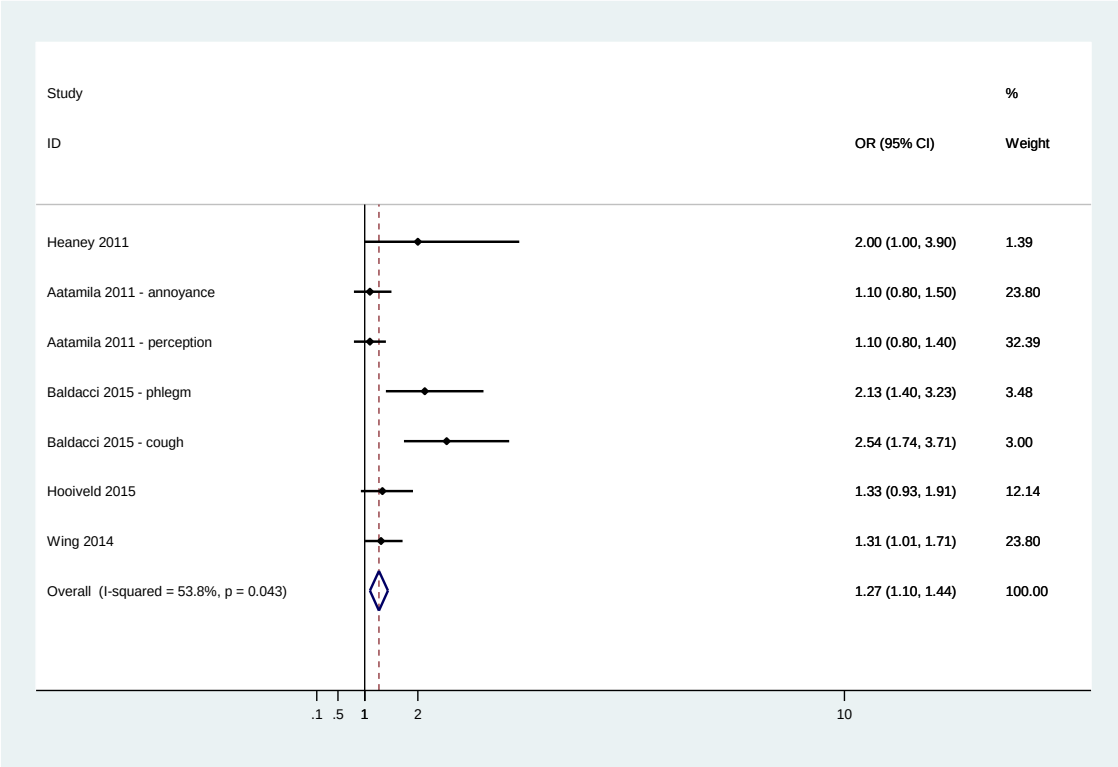
There were no observed differences between groups for the gastrointestinal score among workers (37) (see *Supplementary material; Appendix S15*).

Lower respiratory symptoms

The association of lower respiratory symptoms with odour pollution was evaluated and discussed by 15 studies (7, 12, 18, 19, 29, 31, 34-36, 151, 161, 163, 165, 169, 171). All studies were on adults except one (151). No study was conducted on workers.

Cough and phlegm were the most common outcomes reported in this group. 11 studies reported cough and phlegm as odour-related symptoms (12, 18, 19, 29, 31, 34-36, 161, 163, 171). Meta-analysis showed a pooled effect of 1.27 (95% CI: 1.10-1.44) (see figure 15), with moderate heterogeneity (I^2 = 53.8%, p-value = 0.043) There was no evidence of publication bias (Egger's test, p-value = 0.077). No analysis of subgroups was done due to the low number of studies, and because all studies were based on subjective exposure assessment.

Figure 15. Forest plot of study-specific and pooled Odds Ratio (OR) and 95% Confidence Intervals (95%CI) of residential exposure to odour and lower respiratory symptoms in exposed versus non-exposed subjects.



Among the studies that were not included in the meta-analysis (see *Supplementary material; Appendix S18*), self-reporting of cough/phlegm was significantly higher in the study of *Segala et al.* (18) in the highest exposure categories: odour intolerant vs tolerant (OR = 2.35; 95% CI 1.75-3.15), and in the group with complaints about impacts on health vs no complaints (OR = 1.64; 95% CI 1.15-2.32). In *Aatamila et al*. (29), reports of cough in the past 12 months were significantly higher in the group of residents living closer to the waste site (distance<1.5 km: OR=1.3; 95% CI 1-1.8). Cough was significantly associated with odour frequency and even with odour annoyance after adjustment for odour frequency. However, no direct link was revealed between lower respiratory complaints and odour frequency after adjustment for odour annoyance (31). Increasing reports of cough in the past 12 hours related to 12-hour mean odour were found in *Schinasi et al*. (163).

Among other respiratory symptoms, 9 studies reported exposure objectively (7, 12, 18, 29, 31, 36, 151, 169, 171), mainly with distance as a proxy of exposure. Only 3 studies reported

significant findings (31, 151, 169) for wheezing, asthma and shortness of breath (see *Supplementary material; Appendices S19, S20 and S21*). *Mirabelli et al.* found school proximity within 3 miles of a swine AFO was related to higher physician-diagnosed asthma (PR = 1.07; 95% CI: 1.01-1.14, mostly in non-allergic adolescents PR = 1.14; 95% CI: 1.01-1.26), asthma medication use (PR = 1.07; 95% CI: 1.00-1.15), asthma-related visit to a physician or an emergency department or hospitalization (PR = 1.06; 95% CI: 1.00-1.12) (151). Nevertheless, no clear association was found for current wheezing (PR: 1.04; 95% CI: 0.99–1.09) or frequent severe wheezing (PR = 1.02; 95% CI: 0.97–1.07) in *Mirabelli et al.* (see *Supplementary material; Appendices S19 and S20*) (151). Other respiratory symptoms, such as chest pain, COPD and respiratory infection were hardly reported among studies, and they used different approaches for the distance (see *Supplementary material; Appendices S22, S23, S26 and S27*). No consistent associations were found between distance to the odorous source and COPD (12, 18), respiratory infections (18, 29), or chest pain (7, 29, 169).

Among studies evaluating exposure subjectively (18, 19, 29, 34, 35, 151, 161, 163, 165, 169, 171), 8 reported significant health effects (18, 19, 29, 35, 151, 161, 163, 165). Most consistent estimates were reported for asthma (18, 35, 165), while associations with wheezing were weaker (see *Supplementary material; Appendices S19 and S20*). *Wing et al.* (161) showed odour from livestock facilities was significant related to difficulty breathing (PR = 1.52, 95% CI: 1.02-2.27) and increased the lower respiratory diseases score (mean difference = 0.28, 95% CI: 0.05-0.5) for *moderate/strong/very-strong odour perceived* compared to *none or faint odour perceived*. Nevertheless, most associations reported by *Wing et al.* extended a range which included both a protective and the risk effect. According to *Segala et al.* (18), people complaining about odour intolerance had a higher prevalence of self-reported respiratory infections (OR = 4.81, 95% CI: 3.24-7.14) and COPD (OR = 2.95, 95% CI: 1.84-4.73). Similar findings were found for the group with complaints about impacts on health vs no complaints for COPD (OR = 2.05; 95% CI 1.21-3.49), although the effect size precision was low (18). There is also a higher risk of enduring cough and COPD in people complaining about odours in terms of a health threat, nonetheless, the precision of 95% CIs is lower in this sense (see *Supplementary material; Appendix S23*) (18). No association was found between odour and chest pain in the included studies (see *Supplementary material; Appendix S26*) (7, 29, 36, 163, 169, 171). In *Schinasi et al.*, regression coefficients from chest tightness, wheezing severity score and phlegm had positive value beta estimates, but their CIs included the null value (163).

Reports of shortness of breath and difficulty breathing in the previous 12 hours were significantly associated with 12-hour mean odour (163). In *Steinheider et al.* (*Nörvenich* study), difficulty breathing was also significantly associated with log odour frequency (31) (see *Supplementary material; Appendix S21*).

Only two studies evaluated lung function and bronchial hyperresponsiveness (163, 165). A reduction in PEF and FEV_1 with increasing odour was found in both studies (163, 165); however, 95% CIs included the null value. In addition, no associations were seen between self-reported odour annoyance and bronchial hyper-responsiveness to methacholine (165).

Upper respiratory symptoms and allergies

10 studies (18, 19, 29, 34, 36, 37, 161, 163, 169, 171) presented data regarding associations between odours and upper respiratory symptoms. All studies were on adults. Only one study was conducted on workers (37). Appendices S28 and S29 provide details on the measured data and associations reported in the individual studies that correspond to the data described below.

Regarding studies with objective exposure (18, 29, 36, 37, 169, 171), no consistent associations were found between distance zones and frequency of cold/flu, runny nose, nasal congestion and non-allergic rhinitis (18, 29, 36, 169, 171).

When it comes to the studies with subjective exposure (18, 19, 29, 34, 161, 163, 171), only in three (18, 34, 163) a significant effect of odour was found, with an increased risk for runny nose. In *Heaney et al.* (34), there was a significantly higher frequency of runny nose in people reporting odour (OR = 2.6, 95% CI: 1.4–4.9). In *Segala et al.*, (18) the higher risk of experiencing runny nose was found both in people with self-reported chemical intolerance (OR = 2.1, 95% CI: 1.59-2.78), and in people complaining about malodour in terms of a health threat (OR = 1.69, 95% CI: 1.22-2.32). A borderline association was found between cold/flu in last month and odour annoyance (19) (OR = 1.38, 95% CI: 0.97-1.99). Finally, In *Schinasi et al.* (163), positive beta value estimates suggested the presence of a risk effect of exposure on self-reported runny nose. No consistent associations were found between self-reported odour annoyance and frequency of cold/flu in *Hooiveld et al*. (19)

In the only study conducted on workers, there were no significant differences between the flu score in exposed subjects and the control group (37).

4 studies evaluated the effect of odour on the immune system and allergic sensitization by estimating IgE and IgA concentration and an allergy score obtained by questionnaires, using self-reported exposure (15, 165) or objective exposure (37, 169), but no association with increasing odour exposure emerged (see *Supplementary material; Appendix S30*).

Mucous membrane irritation and skin disorders

12 studies evaluated odour effect on mucous membrane irritation (12, 16, 18-20, 29, 34, 36, 161, 163, 169, 171). 6 studies were conducted on skin disorders (7, 29, 34, 161, 163, 169). All studies were on adults. No study was conducted on workers. The symptoms considered in the studies were: eyes irritation, sore throat/burning throat, nose irritation, general irritation symptoms, skin irritation/itchy eczema. Appendices S31, S32, S33, S34 and S35 provide details on the measured data and associations reported in the individual studies that correspond to the data described below.

Regarding studies with objective exposure, 6 studies evaluated the occurrence of irritation symptoms objectively by distance zones (7, 12, 18, 29, 36, 169) and significant odour effects were found related to prevalence of dry throat past 12 months (29, 169), nose irritation (29), and skin irritation (169).

Regarding studies with subjective exposure (16, 18-20, 29, 34, 161, 163, 171), significant findings were detected for eye irritation/burning eye in 5 studies (18, 20, 29, 34, 163), for sore throat/dry throat/burning throat in 5 studies (18, 20, 29, 34, 163) (both odour tolerance and perception), for nose irritation/burning nose in 2 studies (34, 163), for nose/eye irritation symptoms in one study(16), and for skin irritation/rash in three studies(34, 161, 163). In this respect, it is worth mentioning some of the results hereunder.

- In *Heaney et al*., twice-daily odour reports were associated with eye irritation (OR = 5.3; 95% CI: 2.5-11.6), burning nose (OR = 5; 95% CI: 2.5-10.2), burning throat (OR = 3.3; 95% CI: 1.5-7.1) and skin irritation (OR=4.7; 95% CI: 1.1-21) in the previous 12 hours (34). Nonetheless, associations tend to be imprecise due to the wide range of the confidence interval for all outcomes.

- In *Schinasi et al.*, the log odds of eye nasal and throat irritation following 10 minutes outdoors increased significantly (OR= 1.70, 95% CI: 1.51-1.9; OR= 1.92, 95% CI: 1.74-2.11; OR= 1.51, 95% CI: 1.34-1.70; respectively), for every unit increase in odour (163).
- In *Aatamila et al*., only residents who were classified as "annoyed by odour" tended to report eye irritation (OR = 1.5; 95% CI: 1.1-2.1) and dry throat (OR = 1.5; 95% CI: 1.1-2) more than the residents who were ''not annoyed''(29). However, the effect of odour perception on irritation symptoms was weak.
- In *Segala et al*., responders reported elevated ORs for eye irritation and dry throat when associated with odour tolerance and odour perception (18).
- There were no consistent findings for acute irritation outcomes by odour annoyance in *Hooiveld et al*. (19).
- In appendix S34, associations reported by *Sucker et al.* showed that there was a significant impact of odour annoyance in general irritation symptoms ("residents with irritant symptoms": OR = 1.5; 95% CI: 1.4–1.7) (16). This model was expanded by odour hedonic tone, odour frequency and odour intensity as extra independent exposure variables. Nevertheless, none of them had further influence (16). The magnitude of associations between twice-daily odour and acute irritation symptoms was high (OR = 3.7; 95% CI: 2.0-7.1), however, the confidence interval describes the uncertainty due to a wide range of estimated effects.

Mood states

13 studies considered that malodour may have an impact in the mood states (7, 13, 19, 22, 31, 34, 36, 160, 164, 166, 169, 171, 172). All studies were on adults. One study was on workers (160). Appendix S36 provides details on the measured data and associations reported in the individual studies that correspond to the data described below.

6 studies evaluated exposure objectively (7, 13, 31, 36, 166, 169). Significant associations for high exposed residents were only reported for nervousness (OR=2.10; 95% CI: 1.02- 4.30), and difficulty concentrating (OR=2.78; 95% CI: 1.17-6.7) (169). No significant effect was observed in *Blanes-Vidal* for difficulty concentrating when increasing NH_3 exposure, which has been

used as a proxy of odour exposure (13). Additionally, no significant association between sexual difference and residents living near the malodorous site was observed (7).

9 studies evaluated exposure subjectively (13, 19, 22, 31, 34, 160, 164, 171, 172). Significant associations were found for all mood outcomes in *Horton et al.* (164), for nervousness, angriness, stress, unhappiness in *Heaney et al.* (34), and for sadness and stress-related symptoms in *Hooiveld et al.* (19). In *Blanes-Vidal* (13), a dose-response association between odour annoyance and difficulty concentration was found, but not in the study of *Heaney et al.* (34). Specifically, in *Horton et al.* (164), ORs for feeling nervous, gloomy, angry, and unable to concentrate, associated with a 1-unit change in self-reported odour on a 8-point scale, twice daily, were 1.60 (95% CI: 1.41-1.81); 1.43(95% CI: 1.25-1.63); 1.52 (95% CI: 1.37-1.70) and 1.31 (95% CI: 1.16-1.50), respectively. In *Heaney et al*., ORs for feeling stressed, angry/grouchy, gloomy/unhappy, nervous/anxious, increased 2.1 (95% CI: 1.2-3.8); 3.9 (95% CI: 1.8-8.5); 3.1 (95% CI: 1.6-6.1); 2.5 (95% CI: 1.3-5.0), respectively per unit of reported odour during the 5 min outdoors on a 5-point Likert-type scale twice-daily (34). The mean of emotional wellness through SF-12 score (12-item Health Survey) decreased with an increasing level of odour annoyance in *Radon et al.* (172).
Considering the study on workers, participants in the high odour score group reported a higher IES-R score (post-traumatic score) than those in the low odour score group. These associations lasted for at least three years after the pollution was removed (160).

Cardiovascular system signs and symptoms.

Three studies evaluated the effects of odour on cardiovascular symptoms and blood pressure (7, 18, 162). Each unit of odour increase on an 8-point scale was associated with increases in diastolic blood pressure (mmHg) (OR=1.26; 95%CI: 1.08-1.47), but not in systolic blood pressure (OR=1.1; 95%CI: 0.87-1.40) (162). No significant association was found in the other two studies (7, 18). Appendix S37 contains details on the measured data and associations reported in the individual studies.

Odour nuisances

10 studies (12, 13, 16, 20, 28, 31, 36, 164, 169, 171) investigated odour nuisances in the population regarding to their proximity to industries, odour perception, odour frequency or

intensity, hedonic tone and NH_3 exposure. All studies were on adults. No study was carried out on workers. Appendix S38 provides details on the measured data and associations reported in the individual studies that correspond to the data described below.

Regarding studies evaluating exposure objectively (12, 13, 28, 31, 36, 169, 171), a significant association with odour annoyance was found in *Steinheider et al.* (31) (with odour frequency), in *Blanes-Vidal* (13) (with NH_3 concentration), and in *Boers et al*. (28) (with modelled odour exposure). Results from linear regression revealed an increase of the degree of annoyance with odour frequency in the *Nörvenich* study by *Steinheider et al*. (31). Exposure to NH_3 concentration was significantly associated with odour annoyance perceived by the residents. Participants exposed to NH_3 concentrations of 2–3 $\mu g/m^3$ and >3 $\mu g/m^3$ were significantly more likely to report annoyance caused by odours compared to residents exposed to NH_3 concentrations <2 $\mu g/m^3$ (OR = 2.50; 95% CI: 1.55–4.05; for 2–3 $\mu g/m^3$; and OR = 4.17; 95% CI: 2.40–7. 23; for >3 $\mu g/m^3$). Multivariate analysis showed that the main factor associated with moderate, high or extreme odour annoyance responses was the level of NH_3 exposure at the household (OR = 10.59; 95% CI: 1.35–83.13, for each unit increase in Log_eNH_3 exposure) (13). Multivariate analyses from *Boers et al.* (28) showed a statistically significant positive association between modelled P98 odour exposure and reporting of odour annoyance from livestock housings (OR= 2.04; 95% CI: 1.39–3.01), odour annoyance from spreading slurry and manure (OR= 1.63; 95% CI: 1.28–2.08), and livestock farming in general (OR= 1.88; 95% CI: 1.48–2.38).

A significant increase in odour nuisances in the areas that were closest to the odour source was also found in other 3 studies (12, 36, 169). There were significant differences between groups (landfill and comparison households) for reports of *noticing a bad smell in the last 12 months* and *being worried about environmental issues in their neighbourhood* ($p < 0.001$) (12). Using χ^2 tests, there were significant trends across exposure groups (high/low exposed and comparison) and environmental worry categories (169). Significant area trends from χ^2 tests were also found by percentage of respondents who reported being very much bothered by the odour, very much or moderately bothered, and not bothered or odour not noticed (36). However, according to *Deane and Sanders 1977*, there were no clear significant differences in odour annoyance by areas (171).

Regarding studies evaluating exposure subjectively (16, 20, 164), a significant dose–response association between odour and annoyance was found in *Sucker et al.* (16), consistent across the different exposure measure (odour frequency, intensity, hedonic tone), aggravating the effect in severely annoyed subjects. Furthermore, in *Horton et al.* (164), the latter association was consistent across odour sources (livestock housings, slurry and manure, livestock farming in general).

Discussion

Lately, there has been a rising number of concerns about malodourous environmental pollution, with a growing body of epidemiological evidence suggesting that repeated odour exposures may affect health. This systematic review provides the state-of-art on the health effects of odour from industrial sources. To our knowledge, this is the first study attempting to accurately synthesize and integrate the available evidence on this association. We evaluated the outcomes of 29 observational studies. Secondly, we revised all effect size estimates reported from all included studies and analysed those that were amenable to meta-analyse by similar exposure assessment. Finally, we critically appraised the main body of evidence of each individual study.

Meta-analysis results showed that residential odour exposure was associated to an increased risk of headache and cough/phlegm, and to a borderline risk of nausea and vomiting. We found suggestive associations for the other investigated outcomes (e.g., asthma, mucus irritation, mood states), but evidence is sparse. Only two studies were carried out on occupational setting, and they showed a statistically significant higher score of subjective complaints, neurological complaints and post-traumatic stress symptoms in exposed workers than in controls. These associations persisted at least three years after the pollution was removed (37, 160).

The associations with headache, cough/phlegm and nausea/vomiting do have a biological plausibility. Unpleasant odours are able to modulate autonomic system responses, such as vagal nerve inducing nausea or vomiting (21). Another mechanism involves stress, consequent to environmental worry (176), and stress-related psychosomatic reactions such as chronic muscular tension, headaches and sleep disturbance. Chemicals responsible for odour may cause irritation, supporting the higher risk for cough/phlegm. Eye and nose irritation and asthma exacerbations can also be related to this odour-related irritation, but only limited evidence was found in this review. Our review confirms the strong association between odour and annoyance confirming the potential mediation role on odour-related effects. We could not find any information on potential individual effect modifiers such as age, sex, educational level (177).

So far, only one other systematic review is available focused only on exposure from AFO proximity providing little evidence of association between surrogate clinical outcomes and respiratory tract-related outcomes (146, 147). There is a growing public attention on the topic

at an international level as documented by the non-negligible number of studies retrieved in this review. Nowadays, there is also an effort by a variety of countries to classify odour as an atmospheric pollutant and regulate emissions by different policy frameworks worldwide (2).

Methodological considerations

Some limitations of our review should be mentioned. Formal test for publication bias was not carried out due to the limited number of studies included in the meta-analysis, but we cannot exclude this kind of bias and possibly other related biases (e.g., language bias, citation bias, multiple publication bias) (178). However, we expect that the comprehensive literature search, including grey literature, may have limited the impact of publications bias. The inclusion of small studies (less than 100 subjects) in our review suggests this bias is not a main concern. Meta-analytical estimates are affected by a moderate degree of heterogeneity due to differences among studies in terms of sources of exposure, population characteristics, and study length. An additional concern derives from the multiple hypothesis testing that increases the probability of false positive results due to the multiplicity phenomenon, as suggested by other authors (146, 147).

Moreover, the associations between odour and headache, nausea and cough need to be considered with caution due to the overall low quality of the studies, especially related to the methodological problems of the observational study design.

Study design

The majority of studies included in this review had a cross-sectional design (n=23), limiting conclusions about causal and temporal associations (12, 13, 29, 35, 160, 161, 172). They may provide a first hint of a hypothesized cause of a disease, but this is not a proof of causality (13, 179). Observational studies, particularly cross-sectional epidemiological studies, serve a great purpose in adding new knowledge, reporting potential relationships that lead to further explorations (180).

6 studies used a panel approach, commonly used in air pollution epidemiology (181), representing one of the best options to study short-term health effects of odour, although they can be affected by the drop-out bias and limited statistical power. Studies used conditional fixed-effects models in which participants serve as their own control (15, 34, 162-164, 167).

The temporal nature of this analytical method eliminates confounding from measured and unmeasured time-independent factors that differ between people, although it still could have either attenuated or exaggerated associations due to time-related confounding. For this reason, all panel studies adjusted for time of day, which helps reduce any time-related confounding by diurnal covariation. However, the external validity of the results is limited with this design (163).

Exposure assessment

Analytical methods to assess odour exposure in communities differ drastically between studies. Most objective techniques (7, 12, 13, 18, 28, 29, 31, 33, 36, 151, 169, 171) to assess odour exposure are unable to include the element of human sense of smell (6, 114, 182, 183). The European Standard defined an objective procedure for the measurement of odour concentration using a dynamic olfactometry assessed by a panel of human (94). We found two studies, which followed a systematic standard method for the assessment of odour frequency through panellist testing and olfactometers (16, 31). Subjective exposure measures, such as odour rating and scores provided by participants, increased the likelihood of bias (6, 184, 185). Self-reported exposure is well known to be affected by information bias. Several studies supported the theory that odour intensity does not influence directly annoyance and symptoms, but instead these relations are mediated by perceived odour pollution, health risk perception and other person-related factors, such as, age, sex or educational level, stress, exposure history, physiological factors… (3, 9, 11-13, 15-21, 28).

In this sense, it should be considered that the methods for assessing odour exposure should include also individual perceptions as effect modifier on odour impact on a population (6). Odour perception, intolerance or annoyance or complaint (7, 18-20, 29), are adequate indicators to this aim.

One thing clear in this matter is that most experts agreed in pointing out the assessment of odour annoyance as very complex task, due to the nature of the exposure itself and the lack of analytical methods that would allow to match the sensitivity, the speed of response and the breadth of application of the human nose (3, 6, 114). Some of these studies have used distance as a proxy of odour exposure (7, 12, 18, 29, 31, 36, 151, 186) and the *Nettetal study* in *Steinheider et al*. (31). In our results, no consistent evidence of effects in the reporting of

somatic symptoms was found by distance to the source of exposure. In *Nettetal study*, results from *Steinheider et al.* exhibited direct effect between distance to the odour source and symptom reporting, by analysis of covariance, as well as annoyance-mediated association with odour exposure (31). Distance, as a proxy for exposure, has been greatly used in preliminary investigations of the possible health effects associated with odour pollution, as stated by *Pascal et al. 2013*: "*as a way to overcome the lack of measurement data, especially objective, but also to reduce the latency problem*"(187). However, it has been shown to be prone to underestimate associations, as no consideration is given to the seasonal and spatial characteristics (emissions, local meteorological conditions or topographical features, temperature, wind….) all of which play a significant role in determining dispersion, concentration and intensity (13, 19, 28, 29, 160, 188, 189).

Another exposure measure was the ammonia concentration in the air (13). Although the elevated levels of ammonia may cause irritative symptoms (190), the levels considered in the studies are several orders of magnitude lower than exposure limit in the workplace (35 ppm for a short-term (15-minute) exposure limit in the workplace, circa 2000 times higher than the maximum level reported in *Blanes-Vidal* (13). There is a need to account that air pollution includes a variety of chemicals at low concentrations, so the use of ammonia as a surrogate for odour pollution, as clearly stated by the authors, may represent a great limitation (13, 33).

Overall, included studies agreed on pointing the importance of using a standard objective method for exposure and outcome assessment in environmental epidemiology (3, 6, 13, 28, 160, 165). In fact, some authors ended up mentioning dispersion modelling as a way out of this methodological issue (188, 189). *Boers et al.* was the only study that used air dispersion modelling as a proxy of odour exposure, suggesting that it could be a good substitute of odour annoyance to objectively predict odour concentrations, and to evaluate its health effects on residents (28).

Outcome assessment

Outcomes were mainly based on self-reported information. Only 4 out of 29 studies used objective outcome measurements such as lung/bronchial function (163), immune function and allergy (15), blood pressure (162), bronchial hyperresponsiveness to methacholine (165). Most studies have lacked medical objective assessments and generally depended on participants'

recall of symptoms over different periods that go from weeks to over the last 12 months. There are potential sources of recall bias, particularly when using a subjective approach to assess health outcomes, such as negative mood states due to bad smell, health risk perceived, or environmental worrying, which could lead to a higher tendency to report symptoms and reduce the precision of the effect estimates (13, 19, 20, 29, 34, 160, 162, 165). In case where a study was based on outcome and exposure that were both self-reported, it might have occurred that the exposed subjects, experiencing unpleasant odours, were also more worried about their health and therefore more prone to reporting health symptoms than the non-exposed subjects. This created the case for differential misclassification of the outcome. In addition, respondents may have been more likely to recall difficulty in correctly remembering recent events, also known as seasonal bias, related to the amount of time that has elapsed (12). Some studies tried to reduce possible recall bias by not mentioning odour when presenting the survey, or by utilising memory aids to help remember symptoms (29, 161).

Response bias is a concern in most included surveys, both in terms of low participation rates and missing data to specific questions. That is why, future studies should attempt to address this issue by ensuring adequate response rates to the study, or by controlling for non-response e.g. by weighting methods (34, 162, 191, 192).

Confounding

Regarding confounding, there are two aspects that are worth noting. Of all included studies, the most prevalent source of odour pollution was AFOs and waste treatment sites. Therefore, air pollution exposure from these industrial activities may be common. Additionally, the adjustment for concurrent environmental exposures is crucial to disentangle odour-related effects. In the present review, few studies adjusted for other environmental stressors, such as noise, traffic, bioaerosols, pesticides (16, 19, 151, 161), while only one stratified the population to isolate the odour-only exposed group (7). These may interfere and reduce precision of the studies (15, 19, 28, 29). One of the included panel studies was downgraded to a high risk of bias (167) since it failed to make proper adjustments for concurrent environmental exposures.

Four social confounding variables (age, sex, smoking status, educational level and/or SES) were identified and considered as key confounders due to their potential relationship with health symptoms. Nonetheless, there is an overall consensus in stating that other stressors may also

influence the association between odour and the occurrence of health symptoms. Another issue emerging from the review is that many included studies only assessed confounders and co-occurring exposures were by self-reports.

Quality of the evidence

We used the approach proposed by the US National Toxicology Program (152, 153), one of the emerging approaches in the environmental (and occupational) health context, to evaluate the risk of bias of the body of evidence. Overall, 15 out of the 29 studies had a high risk of bias due to the limited confounding control and exposure and outcome misclassification, since most studies used self-reported information. On the contrary, 5 studies were at low risk of bias and the remaining 9 showed an intermediate risk.

There are limitations with included studies which may affect the strength of our results. The inclusion of only non-randomized studies, small sample sizes and significant differences in baseline characteristics of cohorts among studies (heterogeneity) may lead to large differences in the interpretation of the results and establishment of conclusions.

One key factor which may affect the conclusions our review is the meta-analysis of observational studies. The increased heterogeneity observed among studies may introduce bias in the summary effect (the diamond). Despite the intents to mitigate the risk of confounding and selection bias, adjusting for several characteristics or using propensity scores, observational studies have a limited internal validity. Additionally, within observational studies, no causal or temporal relationship can be proved, and there is a high risk of selective reporting bias due to protocol and preregistration are rarely published (193).

Language restriction, the fact that many important papers get published only in local medical journals, or the tendency to only publish results that are statistically or clinically significant may also pose a potential risk of publication bias. Indeed, funnel plot and Egger's test reveal asymmetry trends and indicate potential publication bias. The absence of larger studies may be one of the main reasons for this to happen. Small studies tend to report higher effects.

Most of the included studies had short follow-up periods and primary outcome measures were highly variable across the included studies. The timelines for reporting outcomes vary

considerably among the included studies. The gathered information ranges from outcomes experienced over the previous 7 days to along 12 months.

Implications for public health and policy making

As is known, good environments provide benefits to health and well-being. Conversely, air pollution, malodour, noise, chemicals, radiation, poor quality of water and climate change are estimated to be responsible for 15–20% of the global burden of disease (194, 195). Within this context, there is a clear need for an integrated multi-sectoral approach to addressing environmental challenges effectively, particularly in odour pollution, by implementing long-term policies that reduce the risks to health.

However, as has been clearly stated in this manuscript, disparities in definitions and criteria regarding environmental regulations continue to vary significantly among European countries, despite the efforts for implementing a common multi-level governance model in this matter.

A recent European study collected all the existing laws and regulations in efforts to address the management of odour impact on the communities, finding a heterogeneous picture (EU Project D-NOSES). Europe has included odours in the European Directive on industrial emissions (Directive 2010/75/EU)(140), but at national level, laws and environmental guidelines are in place only in some countries, such as Italy (Legislative Decree 152/2006). Nevertheless, no specific public-health guidance is still available. Wider considerations of odour exposure are expected to increase with increasing urbanization (6), e.g., due to waste disposal sites or intensive farming. It is clear that the effective prevention and response to protect public health is a matter of urgency. Addressing the odour problem is also an equity issue, since neighbouring residents of odour-polluted sites are most likely low-income groups, as it happens for air pollution (196).

Findings from this systematic review underline the public health importance of odour pollution for population living nearby industrial odour sources. However, we cannot draw strong conclusions for public health recommendations or policy making out of the studies included. In spite of that, this study provides experience to draw recommendations for future research in the field (see *Future research directions* section).

Considering the large implications of odour pollution, mainly on neighbouring residents living in the vicinity of odour sources, and the growing efforts in regulating odour pollution, it is necessary to define reliable standardized methods to estimate its effects on population health, and to provide evidence-based guidance to bridge the gap from a public health perspective.

Future research directions

There is substantial evidence for the impact of odour on health-related symptoms (e.g., headache, nausea and cough). Nevertheless, epidemiological studies conducted in this matter showed inconsistent results with a probably high risk of bias due to study characteristics, such as the study design, statistical analysis, exposure and outcome assessment and the lack of adjustment for important confounders and co-exposures. Below, I have listed some key points for future research studies on odour pollution exposure and impact on health.

Related to the exposure:

- An objective, standard method to estimate odour exposure taking into account for perceived odour, perceived health risk and co-exposures, such as noise and air pollution, has not yet been defined (see *Exposure assessment* section).

Related to the outcome:

- The reliability of recall patient-reported outcomes may be limited. Providing an objective clinical measurement to estimate a dose-dependent effect of odour exposure could minimize bias (see *Outcome assessment* section)

Related to the study design and analysis plan

- The target population may be expanded to include other vulnerable groups: children, pregnant women, workers and elderly, so that the consistency of the evidence can increase (see *Study design* section).
- There is a need for further studies in the role of odour annoyance as a potential mediator in the association between odour exposure and health status is needed (see *Confounding* section).

Related to the evaluation of the quality of the evidence:

- There should be a gold standard RoB tool which would allow for evaluation of the quality of observational studies in environmental health (see *Quality of the evidence* section).

Conclusions

In this systematic review and meta-analysis, we summarized the current knowledge on health effects of exposure to odour pollution from industrial sources. Several outcomes and surrogate endpoints have been examined in order to measure its effect and to assess its biological plausibility in the population object of study.

This study provides considerable support for the scientific conclusions adopted in The Distributed Network for Odour Sensing, Empowerment and Sustainability (D-NOSES) project and suggests additional suitable health outcomes to be associated with odour pollution. Among the major findings to date are the following:

1. Both residential and occupational exposure have been studied, nevertheless, only two studies involved an occupational exposure assessment in their study design Therefore, no conclusions could be made in this matter. Regarding the effects of residential odour exposure, even though a variety of estimates of the harms of odour pollution for health have been published and included in this study, evidence is still limited for potential effects of odour exposure in the health status of the exposed population.
2. Only 29 studies met the criteria of minimum methodological quality that was necessary for inclusion after an acute screening. Only 9 manuscripts were included in the quantitative synthesis.
3. 98 outcomes were reported at least once. Elevated prevalence of odour-related symptoms, such as headache, cough/phlegm, nausea/vomiting, wheezing and asthma, have been observed among the population that is exposed to industrial activities within the included studies. Given the lack of objective exposure and outcome assessment in the included studies, comparison of individual effects was limited, and results were mainly presented only descriptively.
4. The meta-analysis was only feasible to be conducted for 3 outcomes, observing a significant association between residential odour exposure and headache, cough/phlegm, and poorly associated with nausea/vomiting, which was of borderline statistical significance.
5. For other outcomes such as asthma/wheezing, mood states and mucus irritation symptoms, among others, there are reasonable grounds to believe that increased and

prolonged exposure to odour pollution may be associated with a higher prevalence of asthma-related symptoms, mood-related signs and mucus irritation. At this point, it should be noted that the number of studies did not allow for a quantitative synthesis for these outcomes.

6. Regarding the quality of the studies included, potential sources of measurement errors, the fact that health outcomes were only based on self-reported information, limited our conclusions about the dose-response patterns. In line with the previous critical reviews on this topic, our findings identified an evident mechanism relevant to biological plausibility of the association between exposure to odour pollution from industrial sources and the health status of the population.
7. This review fills a research gap because there is only one other review that used a systematic approach to this field. The systematic review approach allowed performing a valid, reliable and reproducible scientific literature synthesis with people with relevant expertise, such as the Cochrane Trial Search Coordinator. Moreover, different bibliographic databases were used to encounter odour-related health effects in the general population, and to evaluate the variability of studies assessing the odour impact from a wide variety of industrial sources. Additionally, the OHAT tool was applied to assess the quality of the included studies, and the overall body of evidence. No gold standard is available for evaluating the quality of observational studies, especially in environmental health. However, this review shows that the OHAT tool could be helpful for this task.
8. The overall evidence is of "low"- "very low" quality, supporting the need of higher quality studies, especially regarding the study design (e.g., panel studies), the exposure assessment (e.g., dispersion models) and the outcome assessment (e.g., objective measures). In particular, the odour effect needs to be adjusted for the individual perception or annoyance; otherwise, the association could be biased. Most studies pointed out that odour annoyance and symptoms could be mediated by perceived odour and health risk, and other person-related factors.

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Appendices

Appendix S1. Key words for effective screening and removal of records during first stage

Key words		
"In vitro"	Food	Parasite*
"In vivo"	Fragrances	Pathogen*
Agriculture	Fungal*	Perfume
Albumin	Gene*	Pheromone*
Animal*	Genetic*	Phylogen*
Antibiotic*	Genomic*	Pig*
Aquatic	Genotype	Plankton
Bacteria*	Globulin*	Plasma
Biochemical	Heat-Shock	Polymorphism*
Biopsy	Hemo*	Poultry
Calcium*	Hormone*	Protein*
Catheter*	Insect*	Proteomic*
Cell*	Kinase*	Radiologic*
Chemic*	Kinetic*	Rat*
Chicken*	Laboratory*	Redox
Cloning	Learning	Resuscitation
Computer	Leave*	RNA
Diagnostic	Lipid	Sheep*
DNA	Lupus*	Tetraplegia
Doppler	Metabol*	Tissue
Dynamic*	Metabolism	Toxic*
Egg*	Microb*	Transcript*
Electric	Microbiome	Troponin
Embryo*	Microscop*	Turtle*
Encoding	Necrosis	Virology
Farm	Neonate*	Virus
Fertility	Organ*	
Fever	Oxidative*	
Field	Oxygen	

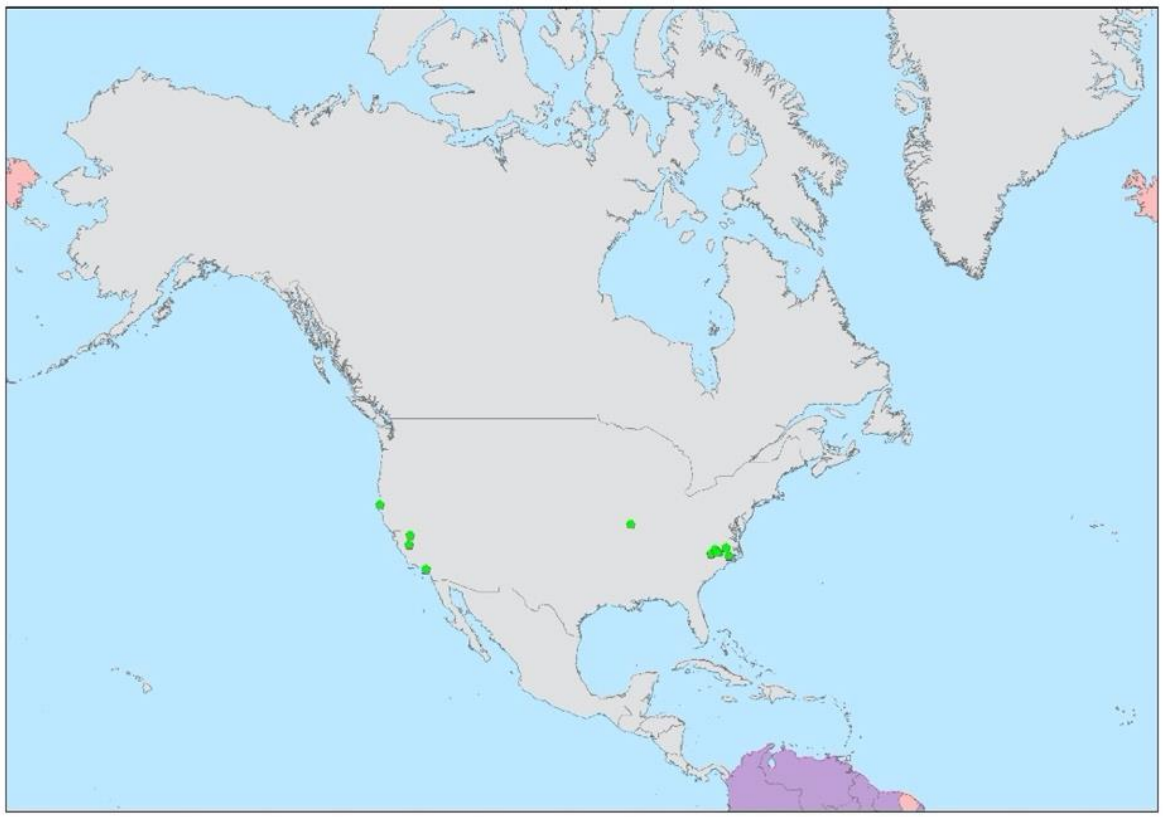
Appendix S2. Characteristics of excluded studies

Study	Reason for exclusion
Aatamila et al., 2010 (30)	Duplicated with another publication or used the same database
Ahlstrom, Berglund, & Berglund, 1986 (197)	Not resident outcomes
Axelsson et al., 2013 (198)	Not resident outcomes
Behbod et al., 2014 (199)	Exposure assessment related to a toxic chemical exposure
Blanes-Vidal et al., 2014 (11)	Duplicated with another publication or used the same database
Claeson et al., 2013 (185)	Study design
Colligan et al., 1979 (200)	Setting. Exposure
Dzaman et al., 2009 (201)	Not resident outcomes
Eltarkawe & Miller, 2018 (202)	Not resident outcomes
Fielder et al., 2000 (203)	Setting. Exposure
Gudziol et al., 2007 (204)	Not resident outcomes
Guidry et al., 2015 (205)	Studies did not capture an specific exposure to an environmental odor from industrial sources
Haahtela et al., 1992 (206)	Exposure assessment related to a toxic chemical exposure
Hangartner, 1980 (207)	Study design
Heaney et al., 2010 (208)	Duplicated with another publication or used the same database
Ivens et al., 1997 (209)	Setting. Exposure
Jaakkola et al., 1999 (210)	Exposure assessment related to a toxic chemical exposure
Jaakkola et al., 1990 (211)	Exposure assessment related to a toxic chemical exposure
Karakis et al., 2009 (212)	Setting. Exposure
Kilburn, 2012 (213)	Exposure assessment related to a toxic chemical exposure
Logue, Ramaswamy, & Hersh, 2001 (214)	Study design
Marttila et al., 1996 (215)	Exposure assessment related to a toxic chemical exposure
Marttila et al., 1994 (216)	Exposure assessment related to a toxic chemical exposure
Mosquera-Becerra, Gomez-Gutierrez, & Mendez-Paz, 2009 (217)	Qualitative evaluation
Nicolle-Mir, 2012 (218)	Duplicated with another publication or used the same database
Osterberg et al., 2007 (219)	Setting. Exposure
Ou et al., 2018 (220)	Setting. Exposure
Partti-Pellinen et al., 1996 (221)	Setting. Exposure
Perrin, 1987 (222)	Study design
Rethage et al., 2006 (223)	Foreign language
Spitzer, Suissa, & Eastridge, 1986 (224)	Setting. Exposure
Steinheider, 1999 (225)	Duplicated with another publication or used the same database
Steinheider, Both, & Winneke, 1998 (226)	Foreign language
Steinheider et al., 1993 (173)	Foreign language

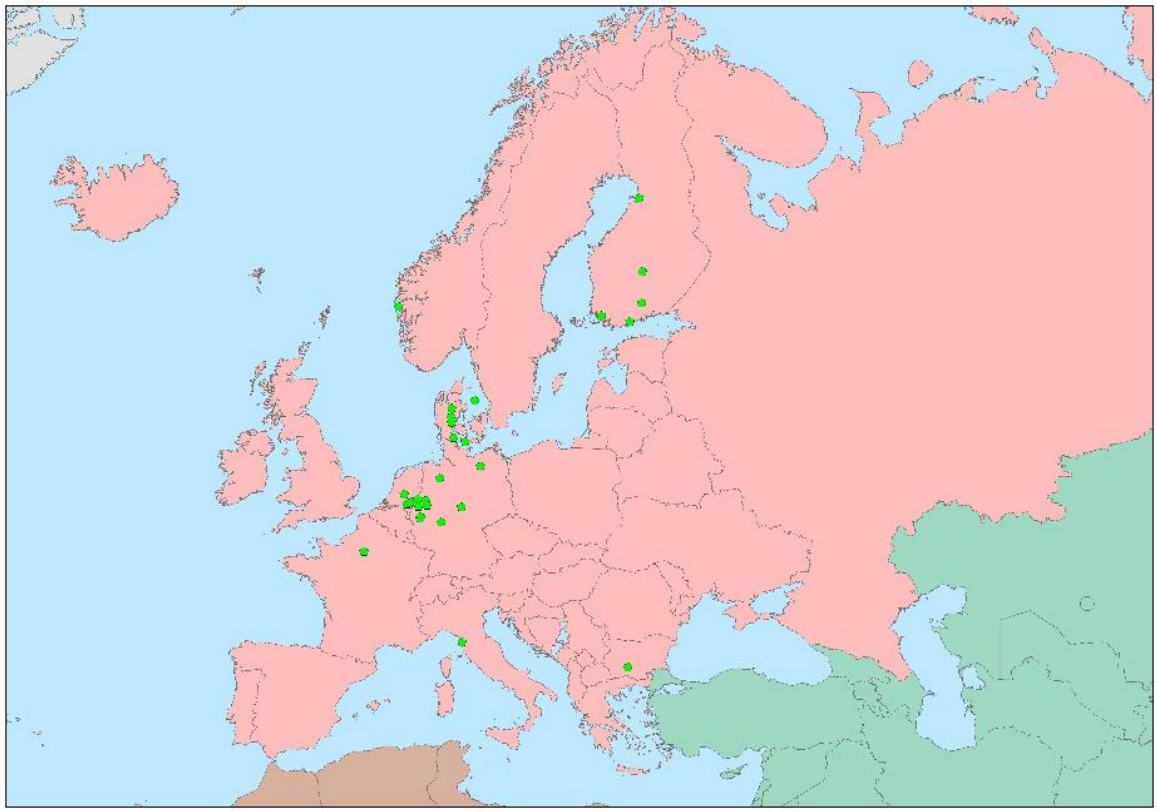
Appendix S2. Characteristics of excluded studies, Continued

Study	Reason for exclusion
Sucker et al., 2008 (17)	Duplicated with another publication or used the same database
Tajik et al., 2008 (227)	Qualitative evaluation
Tjalvin et al., 2018 (228)	Duplicated with another publication or used the same database
Turnovska et al., 1996 (229)	Foreign language
Van Den Hazel & Waegemaekers 1992, (32)	Not resident outcomes
Wing et al., 2008 (230)	Not resident outcomes
Winneke, Neuf, & Steinheider, 1996 (231)	No intervention
Blanes-Vidal et al., 2012 (33)	Not resident outcomes
Herr et al., 2003 (232)	Duplicated with another publication or used the same database
Barnett, 2002 (233)	Abstract not present (Full-text screening needed). Study design
Jackson, Rosales-Guevara, & Blake, 2014 (234)	Abstract not present (Full-text screening needed). Study design
Melamed, 2006 (235)	Abstract not present (Full-text screening needed). Study design
Nelson & Robinson, 2002 (236)	Abstract not present (Full-text screening needed). Study design

Appendix S3. Geographic distribution of the selected studies. North America



Appendix S4. Geographic distribution of the selected studies. Europe



Appendix S5. Headache

HEADACHE: 16 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient log odd (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Subj	Subj	Headache previous 12 hours	Any odour in previous 12 hours graded 0 to 9	0,12	-0,12	0,36
Steinheider et al. 1998 (Nörvenich study)	AFO	Subj	Obj	Headache (7-point scale)	log (odour frequency from observation panel)	0,40	0,02	0,79
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Headache past 2 years	log e (NH3 exposure)	0,25	-0,21	0,70

Effect size was reported as an odds ratio (OR) or Prevalence Ratios (PRs)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Headache past 2 years	Odour annoyance	Not annoyed	1		
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Headache past 2 years	Odour annoyance	Very or extremely annoyed	3,65	1,27	10,5
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Headache past 2 years	Odour annoyance	Moderately annoyed	2,81	1,08	7,3
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Headache past 2 years	Odour annoyance	Slightly annoyed	1,4	0,74	2,65
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Headache past 2 years	NH3 exposure, µg/m3	<2	1		
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Headache past 2 years	NH3 exposure, µg/m3	2–3	1,42	0,75	2,69
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Headache past 2 years	NH3 exposure, µg/m3	>3	1,05	0,5	2,22

Appendix S5. Headache, Continued

HEADACHE: 16 studies									
GENERAL POPULATION: ADULTS									
Effect size was reported as an odds ratio (OR) or Prevalence Ratios (PRs)									
Study	**Source**	**Type of outcome**	**Type of exposure**	**Outcome variable**	**Exposure variable**	**Subcategory**	**Value**	**95% CI inf**	**95% CI sup**
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Headache past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Headache past 12 months	Distance (km)	1.5-3	1,1	0,7	1,7
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Headache past 12 months	Distance (km)	<1.5	1,1	0,8	1,5
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Headache past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011°	Waste treatment + composting	Subj	Subj	Headache past 12 months	Odour perception	Yes	1,4	1	1,8
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Headache past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011°	Waste treatment + composting	Subj	Subj	Headache past 12 months	Odour annoyance	Yes	1,2	0,8	1,7
Heaney 2011	Landfill	Subj	Subj	Headache previous 12-hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011°	Landfill	Subj	Subj	Headache previous 12-hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	3,3	1,5	7,4
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Headache past month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015°	AFO	Subj	Subj	Headache past month	Odour annoyance	Yes	1,1	0,76	1,58
Segala 2003	Wastewater treatment	Subj	Obj	Headache past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Headache past 12 months	Distance (km)	1.5-3	1,07	0,87	1,31
Segala 2003	Wastewater treatment	Subj	Obj	Headache past 12 months	Distance (km)	<1.5	1,09	0,87	1,36
Segala 2003	Wastewater treatment	Subj	Subj	Headache past 12 months	Odour tolerance	Tolerants	1		
Segala 2003	Wastewater treatment	Subj	Subj	Headache past 12 months	Odour tolerance	Moderately tolerants	1,62	1,35	1,93
Segala 2003	Wastewater treatment	Subj	Subj	Headache past 12 months	Odour tolerance	Intolerants	2,64	2	3,5

Appendix S5. Headache, Continued

HEADACHE: 16 studies									
GENERAL POPULATION: ADULTS									
Effect size was reported as an odds ratio (OR) or Prevalence Ratios (PRs)									
Study	**Source**	**Type of outcome**	**Type of exposure**	**Outcome variable**	**Exposure variable**	**Subcategory**	**Value**	**95% CI inf**	**95% CI sup**
Segala 2003	Wastewater treatment	Subj	Subj	Headache past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Headache past 12 months	Odour perception	Complaints but sense impact in health	1,06	0,85	1,33
Segala 2003	Wastewater treatment	Subj	Subj	Headache past 12 months	Odour perception	Complaints with impacts on health	2,04	1,46	2,84
Wing 2014	Sewage treatment and AFO	Subj	Subj	Headache last 6 months	Reported odour of liquid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Headache last 6 months	Reported odour of liquid sewage treatment	None or faint	0,98	0,81	1,18
Wing 2014	Sewage treatment and AFO	Subj	Subj	Headache last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/very strong	1,01	0,77	1,33
Wing 2014	Sewage treatment and AFO	Subj	Subj	Headache last 6 months	Reported odour of solid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Headache last 6 months	Reported odour of solid sewage treatment	None or faint	0,97	0,72	1,32
Wing 2014	Sewage treatment and AFO	Subj	Subj	Headache last 6 months	Reported odour of solid sewage treatment	Moderate/strong/very strong	1,05	0,77	1,44
Wing 2014	Sewage treatment and AFO	Subj	Subj	Headache last 6 months	Reported livestock odour	None or faint	1		
Wing 2014°	Sewage treatment and AFO	Subj	Subj	Headache last 6 months	Reported livestock odour	Moderate/strong/very strong	1,03	0,87	1,23
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Headache past 12 months	Odour zones from previous odour survey	Comparison area			
Lipscomb 1991*°	Hazardous waste site	Subj	Obj	Headache past 12 months	Odour zones from previous odour survey	High exposed	3,86	1,72	8,68
Herr 2009	Composting site	Subj	Obj	headache past 2 years	Exposed group living near composting sites and control	Control	1		

Appendix S5. Headache, Continued

HEADACHE: 16 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR) or Prevalence Ratios (PRs)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Herr 2009°	Composting site	Subj	Obj	headache past 2 years	Exposed group living near composting sites and control	EnvExp-2	1,53	0,98	2,37
Shustermann 1991*	Multiple sites (petrochemical, landfill, sewage treatment, rubber industry)	Subj	Subj	Headache	Odour perception	No	1		
Shustermann 1991*°	Multiple sites (petrochemical, landfill, sewage treatment, rubber industry)	Subj	Subj	Headache	Odour perception	Yes	5,0	3,3	7,7

** Unadjusted models*

° Included in the meta-analysis

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Main results
Georgieff 1999	Paper plant	Subj	Obj	Headache	Distance (km)	No difference between areas
Kret, J., et al. 2018	Landfill	Subj	Obj	Headache	Distance (Exposed area vs not exposed area)	No difference between areas
Steinheider et al. 1998 (Nettetal study)	Fertilizer manufacturing plant	Subj	Obj	Headache	Distance (adjustment for odour annoyance)	No difference between areas
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Headache	Distance (3 areas)	No variation in chi-squared tests was found
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	Headache	Distance (3 areas)/odour annoyance/olfactometry	No difference between areas. For all areas combined, significant variation between headaches and amount bothered by the odour

Appendix S6. Dizziness

DIZZINESS: 8 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Subj	Subj	Dizziness previous 12-hours	Any odor in previous 12 hours graded 0 to 9	0,11	-0,11	0,31
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Dizziness past 2 years	log e (NH3 exposure)	0,10	-0,42	0,61

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Blanes-Vidal, V. 2015	storage and treatment of farming and agricultural waste	Subj	Subj	Dizziness past 2 years	Odour annoyance	Not annoyed	1		
Blanes-Vidal, V. 2015	storage and treatment of farming and agricultural waste	Subj	Subj	Dizziness past 2 years	Odour annoyance	Very or extremely annoyed	6	1,96	18,4
Blanes-Vidal, V. 2015	storage and treatment of farming and agricultural waste	Subj	Subj	Dizziness past 2 years	Odour annoyance	Moderately annoyed	3,5	1,16	10,6
Blanes-Vidal, V. 2015	storage and treatment of farming and agricultural waste	Subj	Subj	Dizziness past 2 years	Odour annoyance	Slightly annoyed	1,02	0,45	2,33
Blanes-Vidal, V. 2015	storage and treatment of farming and agricultural waste	Subj	Obj	Dizziness past 2 years	NH3 exposure, µg/m3	<2	1		
Blanes-Vidal, V. 2015	storage and treatment of farming and agricultural waste	Subj	Obj	Dizziness past 2 years	NH3 exposure, µg/m3	2–3	0,97	0,42	2,23
Blanes-Vidal, V. 2015	storage and treatment of farming and agricultural waste	Subj	Obj	Dizziness past 2 years	NH3 exposure, µg/m3	>3	2,08	0,92	4,69

Appendix S6. Dizziness, Continued

DIZZINESS: 8 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	Study
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Dizziness past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Dizziness past 12 months	Distance (km)	1.5-3	1	0,6	1,5
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Dizziness past 12 months	Distance (km)	<1.5	1,1	0,8	1,7
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Dizziness past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Dizziness past 12 months	Odour perception	Yes	1,1	0,8	1,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Dizziness past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Dizziness past 12 months	Odour annoyance	Yes	1,3	0,9	1,8
Heaney 2011	Landfill	Subj	Subj	Dizzy or lightheaded previous 12-hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Dizzy or lightheaded previous 12-hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	4,1	1,3	12,5
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Dizziness past month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Dizziness past month	Odour annoyance	Yes	1,54	1,02	2,33
Segala 2003	Wastewater treatment	Subj	Obj	Dizziness past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Dizziness past 12 months	Distance (km)	1.5-3	0,8	0,57	1,1
Segala 2003	Wastewater treatment	Subj	Obj	Dizziness past 12 months	Distance (km)	<1.5	1	0,71	1,43
Segala 2003	Wastewater treatment	Subj	Subj	Dizziness past 12 months	Odour tolerance	Tolerant	1		

Appendix S6. Dizziness, Continued

DIZZINESS: 8 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	Study
Segala 2003	Wastewater treatment	Subj	Subj	Dizziness past 12 months	Odour tolerance	Moderately tolerant	1,58	1,19	2,08
Segala 2003	Wastewater treatment	Subj	Subj	Dizziness past 12 months	Odour tolerance	Intolerant	2,88	1,98	4,19
Segala 2003	Wastewater treatment	Subj	Subj	Dizziness past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Dizziness past 12 months	Odour perception	Complaints but sense impact in health	0,94	0,64	1,39
Segala 2003	Wastewater treatment	Subj	Subj	Dizziness past 12 months	Odour perception	Complaints with impacts on health	1,54	0,92	2,57
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Dizziness past 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Dizziness past 12 months	Odour zones from previous odour survey	High exposed	1,66	0,63	4,33
Herr 2009	Composting site	Subj	Obj	Impaired coordination of balance past 2 years	Exposed group living near composting sites and control group	Control	1		
Herr 2009	Composting site	Subj	Obj	Impaired coordination of balance past 2 years	Exposed group living near composting sites and control group	EnvExp-2	3,84	1,41	10,45

** Unadjusted models*

Appendix S7. Sleeping problems

SLEEPING PROBLEMS: 9 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Steinheider 1998 (Nörvenich study)	AFO	Subj	Obj	Trouble sleeping score	log (odour frequency from observation panel)	0,323	-0,0004	0,6464
Steinheider 1998 (Nörvenich study)	AFO	Subj	Obj	Waking up during the night score	log (odour frequency from observation panel)	0,615	0,19948	1,03052
Steinheider 1998 (Nörvenich study)	AFO	Subj	Obj	Not getting enough asleep score	log (odour frequency from observation panel)	0,337	-0,09616	0,77016

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Segala 2003	Wastewater treatment	Subj	Obj	Trouble sleeping past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Trouble sleeping past 12 months	Distance (km)	1.5-3	0,8	0,66	0,98
Segala 2003	Wastewater treatment	Subj	Obj	Trouble sleeping past 12 months	Distance (km)	<1.5	0,98	0,79	1,21
Segala 2003	Wastewater treatment	Subj	Subj	Trouble sleeping past 12 months	Odour tolerance	Tolerant	1		
Segala 2003	Wastewater treatment	Subj	Subj	Trouble sleeping past 12 months	Odour tolerance	Moderately tolerant	1,59	1,33	1,9
Segala 2003	Wastewater treatment	Subj	Subj	Trouble sleeping past 12 months	Odour tolerance	Intolerant	2	1,5	2,65
Segala 2003	Wastewater treatment	Subj	Subj	Trouble sleeping past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Trouble sleeping past 12 months	Odour perception	Complaints but sense impact in health	1,12	0,9	1,39
Segala 2003	Wastewater treatment	Subj	Subj	Trouble sleeping past 12 months	Odour perception	Complaints with impacts on health	1,13	0,8	1,59

Appendix S7. Sleeping problems, Continued

SLEEPING PROBLEMS: 9 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Trouble sleeping past 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Trouble sleeping past 12 months	Odour zones from previous odour survey	High exposed area	2,01	0,95	4,25
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Sleeping problems (people with asthma) past month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Sleeping problems (people with asthma) past month	Odour annoyance	Yes	0,72	0,39	1,33
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Sleeping problems (people with lower back pain) past month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Sleeping problems (people with lower back pain) past month	Odour annoyance	Yes	1,72	1,08	2,76

** Unadjusted models*

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Results
Kret, J., et al. 2018	Landfill	Subj	Obj	Trouble sleeping past 12 months	Distance (km)	No difference between areas
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	Sleeplessness frequent or occasionally	Odour annoyance/distance (3 areas)/olfactometry	No difference between areas
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Sleeplessness reported frequently or occasionally	Distance (3 areas)	No difference between areas
Georgieff 1999	Paper plant	Subj	Obj	Trouble Sleeping	Distance (km)	No difference between areas

Appendix S7. Sleeping problems, Continued

SLEEPING PROBLEMS: 9 studies						
GENERAL POPULATION: ADULTS						
No association estimate in the study						
Study	**Source**	**Type of outcome**	**Type of exposure**	**Outcome variable**	**Exposure variable**	**Results**
Steinheider 1998 (Nettetal study)	AFO	Subj	Obj	Trouble sleeping	Distance from the odour source (adjustment for odour annoyance)	Higher symptom-reporting with increasing distance from the odour source
Steinheider 1998 (Nettetal study)	AFO	Subj	Obj	Waking up during the night	Distance from the odour source (adjustment for odour annoyance)	Higher symptom-reporting with increasing distance from the odour source
Steinheider 1998 (Nettetal study)	AFO	Subj	Obj	Not getting enough asleep	Distance from the odour source (adjustment for odour annoyance)	Higher symptom-reporting with increasing distance from the odour source

Appendix S8. Unnatural fatigue or tiredness

UNNATURAL FATIGUE OR TIREDNESS: 8 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Unnatural fatigue past 2 years	log e (NH3 exposure)	-0,04	-0,51	0,43

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Unnatural fatigue past 2 years	Odour annoyance	Not annoyed	1		
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Unnatural fatigue past 2 years	Odour annoyance	Very or extremely annoyed	3,7	1,28	10,7
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Unnatural fatigue past 2 years	Odour annoyance	Moderately annoyed	3,17	1,18	8,5
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Unnatural fatigue past 2 years	Odour annoyance	Slightly annoyed	0,86	0,42	1,76
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Unnatural fatigue past 2 years	NH3 exposure, µg/m3	<2	1		
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Unnatural fatigue past 2 years	NH3 exposure, µg/m3	2–3	0,89	0,43	1,83
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Unnatural fatigue past 2 years	NH3 exposure, µg/m3	>3	1,05	0,49	2,24
Segala 2003	Wastewater treatment	Subj	Obj	Fatigue past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Fatigue past 12 months	Distance (km)	1.5-3	0,69	0,54	0,88
Segala 2003	Wastewater treatment	Subj	Obj	Fatigue past 12 months	Distance (km)	<1.5	0,54	0,41	0,72

Appendix S8. Unnatural fatigue or tiredness, Continued

UNNATURAL FATIGUE OR TIREDNESS: 8 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Segala 2003	Wastewater treatment	Subj	Subj	Fatigue past 12 months	Odour tolerance	Tolerant	1		
Segala 2003	Wastewater treatment	Subj	Subj	Fatigue past 12 months	Odour tolerance	Moderately tolerant	1,74	1,38	2,18
Segala 2003	Wastewater treatment	Subj	Subj	Fatigue past 12 months	Odour tolerance	Intolerant	2,76	2	3,8
Segala 2003	Wastewater treatment	Subj	Subj	Fatigue past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Fatigue past 12 months	Odour perception	Complaints with no impact on health	0,91	0,6	1,11
Segala 2003	Wastewater treatment	Subj	Subj	Fatigue past 12 months	Odour perception	Complaints with impacts on health	1,37	0,91	2,08
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Fatigue past 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Fatigue past 12 months	Odour zones from previous odour survey	High exposed	2,7	1,02	4,3
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Unusual tiredness past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Unusual tiredness past 12 months	Distance (km)	1.5-3	0,9	0,6	1,4
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Unusual tiredness past 12 months	Distance (km)	<1.5	1,1	0,8	1,5
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Unusual tiredness past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Unusual tiredness past 12 months	Odour perception	Yes	0,9	0,7	1,2
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Unusual tiredness past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Unusual tiredness past 12 months	Odour annoyance	Yes	1,5	1,1	2

Appendix S8. Unnatural fatigue or tiredness, Continued

UNNATURAL FATIGUE OR TIREDNESS: 8 studies									
GENERAL POPULATION: ADULTS									
Effect size was reported as an odds ratio (OR)									
Study	**Source**	**Type of outcome**	**Type of exposure**	**Outcome variable**	**Exposure variable**	**Subcategory**	**Value**	**95% CI inf**	**95% CI sup**
Herr 2009	Composting site	Subj	Obj	Excessive tiredness past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Excessive tiredness past 2 years	Residents near composting site	EnvExp-2	1,87	0,92	2,79
Heaney 2011	Landfill	Subj	Subj	Weary, bushed, exhausted previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Weary, bushed, exhausted previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	1,8	0,8	4
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Fatigue past month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Fatigue past month	Odour annoyance	Yes	1,05	0,72	1,53
** Unadjusted models*									
No association estimate in the study									
Study	**Source**	**Type of outcome**	**Type of exposure**	**Outcome variable**	**Exposure variable**	**Results**			
Kret, J., et al. 2018	Landfill	Subj	Obj	Fatigue past 12 months	Distance (km)	No difference between areas			

Appendix S9. Joint, muscular and back pain

JOINT, MUSCULAR, BACK PAIN: 7 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Subj	Subj	Joint pain previous 12 hours	Any odour in previous 12 hours graded 0 to 9	-0,01	-0,26	0,24
Schinasi 2011	AFO	Subj	Subj	Back pain previous 12 hours	Any odour in previous 12 hours graded 0 to 9	-0,16	-0,43	0,11

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Joint pain past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Joint pain past 12 months	Distance (km)	1.5-3	1,6	1,1	2,4
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Joint pain past 12 months	Distance (km)	<1.5	1	0,7	1,5
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Joint pain past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Joint pain past 12 months	Odour perception	Yes	1	0,8	1,4
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Joint pain past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Joint pain past 12 months	Odour annoyance	Yes	1,5	1,1	2,1
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Muscular pain past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Muscular pain past 12 months	Distance (km)	1.5-3	1,1	0,7	1,5
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Muscular pain past 12 months	Distance (km)	<1.5	1	0,8	1,4

Appendix S9. Joint, muscular and back pain, Continued

JOINT, MUSCULAR, BACK PAIN: 7 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Muscular pain past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Muscular pain past 12 months	Odour perception	Yes	1,2	0,9	1,5
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Muscular pain past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Muscular pain past 12 months	Odour annoyance	Yes	1,5	1,1	2
Segala 2003	Wastewater treatment	Subj	Obj	Joint pain past 12 months	Distance (km)	3-4.5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Joint pain past 12 months	Distance (km)	1.5-3	1,13	0,92	1,38
Segala 2003	Wastewater treatment	Subj	Obj	Joint pain past 12 months	Distance (km)	<1.5	1,11	0,89	1,37
Segala 2003	Wastewater treatment	Subj	Subj	Joint pain past 12 months	Odour tolerance	Tolerant	1		
Segala 2003	Wastewater treatment	Subj	Subj	Joint pain past 12 months	Odour tolerance	Moderately tolerant	1,71	1,43	2,04
Segala 2003	Wastewater treatment	Subj	Subj	Joint pain past 12 months	Odour tolerance	Intolerant	2,68	2,01	3,57
Segala 2003	Wastewater treatment	Subj	Subj	Joint pain past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Joint pain past 12 months	Odour perception	Complaints but sense impact in health	1,03	0,82	1,28
Segala 2003	Wastewater treatment	Subj	Subj	Joint pain past 12 months	Odour perception	Complaints with impacts on health	1,9	1,36	2,65
Herr 2009	Composting site	Subj	Obj	Back pain past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Back pain past 2 years	Residents near composting site	EnvExp-2	1,51	0,97	2,33

Appendix S9. Joint, muscular and back pain, Continued

JOINT, MUSCULAR, BACK PAIN: 7 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Herr 2009	Composting site	Subj	Obj	Joint pain past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Joint pain past 2 years	Residents near composting site	EnvExp-2	1,18	0,74	1,87

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Results
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	Pain in joints	Odour annoyance/distance (3 areas)/olfactometry	No difference between areas and by odour annoyance
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Pain in legs and/or arms	distance (3 areas)	No differences between areas

WORKERS

Effect reported as mean difference between groups

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Tjalvin, G., et al. 2015	Chemical accident	Subjective	Objective	Musculoskeletal complaints score*	Workers living 20–30 km from the explosion site and who were neither employees in the industrial area nor clean-up workers	Controls	0		
Tjalvin, G., et al. 2015	Chemical accident	Subjective	Objective	Musculoskeletal complaints score*	Workers at the time of the explosion and/or clean-up workers	Exposed	1,29	0,06	2,51

** Musculoskeletal complaints score: Headache, Neck pain, Upper back pain, Low back pain, Arm pain, Shoulder pain, Migraine and Pain in the feet experienced past month*

Appendix S10. Other somatic symptoms

OTHER SOMATIC SYMPTOMS: 12 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Subj	Subj	Difficulty hearing previous 12 hours	Any odour in previous 12 hours (9-point scale)	-0,16	-0,61	0,29
Schinasi 2011	AFO	Subj	Subj	Fever previous 12 hours	Any odour in previous 12 hours (9-point scale)	-0,02	-1,06	1,02
Sucker 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Prevalence of General Health Complaints°	log(odour frequency)	-0,11	-0,22	0,10

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Radon 2004	AFO	Subj	Subj	Physical SF-12 score	Odour annoyance	Not at all	1		
Radon 2004	AFO	Subj	Subj	Physical SF-12 score	Odour annoyance	A little	0,52	0,31	0,85
Radon 2004	AFO	Subj	Subj	Physical SF-12 score	Odour annoyance	Very much	0,26	0,12	0,59
Radon 2004	AFO	Subj	Subj	Physical SF-12 score	Odour annoyance	Extremely	0,03	0,01	0,10
Sucker 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Prevalence of General Health Complaints°	Odour annoyance intensity	Pleasant			
Sucker 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Prevalence of General Health Complaints°	Odour annoyance intensity	Not pleasant	1,10	0,90	1,40
Sucker 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Prevalence of General Health Complaints°	Hedonic tone	Pleasant	1		
Sucker 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Prevalence of General Health Complaints°	Hedonic tone	Not pleasant	3,2	2	5

Appendix S10. Other somatic symptoms, Continued

OTHER SOMATIC SYMPTOMS: 12 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Fever past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Fever past 12 months	Distance (km)	1.5-3	1,5	0,9	2,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Fever past 12 months	Distance (km)	<1.5	1,7	1	2,8
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Fever past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Fever past 12 months	Odour perception	Yes	1,3	0,9	1,9
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Fever past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Fever past 12 months	Odour annoyance	Yes	1,7	1,1	2,5
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Toothache past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Toothache past 12 months	Distance (km)	1.5-3	1	0,6	1,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Toothache past 12 months	Distance (km)	<1.5	1,1	0,7	1,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Toothache past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Toothache past 12 months	Odour perception	Yes	1,1	0,8	1,5
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Toothache past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Toothache past 12 months	Odour annoyance	Yes	1,4	1	2,1
Heaney 2011	Landfill	Subj	Subj	General ill feeling previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	General ill feeling previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	2,7	1,1	6,6

Appendix S10. Other somatic symptoms, Continued

OTHER SOMATIC SYMPTOMS: 12 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Heaney 2011	Landfill	Subj	Subj	Ringing in ears previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Ringing in ears previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	2,9	0,6	14,2
Herr 2009	Composting site	Subj	Obj	Frequent urination	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Frequent urination	Residents near composting site	EnvExp-2	1,21	0,68	2,14
Herr 2009	Composting site	Subj	Obj	Flushing or blushing	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Flushing or blushing	Residents near composting site	EnvExp-2	1,2	0,61	2,38
Herr 2009	Composting site	Subj	Obj	Sweating	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Sweating	Residents near composting site	EnvExp-2	1,72	0,98	3,01
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Poor memory	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Poor memory	Odour zones from previous odour survey	High exposed	1,62	0,77	3,41
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Numbness	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Numbness	Odour zones from previous odour survey	High exposed	0,78	0,32	1,91
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Toothache	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Toothache	Odour zones from previous odour survey	High exposed	5,95	1,85	19,16
Hooiveld, M., et al. 2015	AFO	Subj	Subj	General health [5 point Likert scale (bad to very good)]	Odour annoyance	No	1		

Appendix S10. Other somatic symptoms, Continued

OTHER SOMATIC SYMPTOMS: 12 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Hooiveld, M., et al. 2015	AFO	Subj	Subj	General health [5 point Likert scale (bad to very good)]	Odour annoyance	Yes	0,85	0,61	1,18

** Unadjusted models*

° Difficulties falling asleep, waking up during the night, Difficulties falling asleep after waking up, Not getting enough sleep, Headache, Cough, Stomach disorders, breathing difficulties, Feeling miserable

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Main results
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	Difficulty in urinating	Odour annoyance/distance (3 areas)/olfactometry	No difference between areas I, II and III even stratifying by odour annoyance
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	Sick within last 2 weeks	Odour annoyance/distance (3 areas)/olfactometry	No difference between areas I, II and III even stratifying by odour annoyance
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	Doctor visit within last 2 weeks	Odour annoyance/distance (3 areas)/olfactometry	No difference between areas I, II and III even stratifying by odour annoyance
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	Hospitalization within last 2 weeks	Odour annoyance/distance (3 areas)/olfactometry	No difference between areas I, II and III even stratifying by odour annoyance
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	General health [4-point Likert scale (poor to excellent)]	Odour annoyance/distance (3 areas)/olfactometry	No difference between areas I, II and III even stratifying by odour annoyance
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Difficulty in urinating	Distance (3 areas)	No difference between areas
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Sick within last 2 weeks	Distance (3 areas)	No difference between areas
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Saw doctor within last 2 weeks	Distance (3 areas)	No difference between areas
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Hospitalization within last 2 weeks	Distance (3 areas)	No difference between areas

Appendix S10. Other somatic symptoms, Continued

OTHER SOMATIC SYMPTOMS: 12 studies
WORKERS

Effect reported as mean difference between groups

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Tjalvin, G., et al. 2015	Chemical accident	Subj	Obj	Total SHC score d	Workers living 20–30 km from the explosion site and who were neither employees in the industrial area nor clean-up workers	Controls	0		
Tjalvin, G., et al. 2015	Chemical accident	Subj	Obj	Total SHC score d	Workers at the time of the explosion and/or clean-up workers	Exposed	4,07	1,34	6,8
Tjalvin, G., et al. 2015	Chemical accident	Subj	Obj	Neurological complaints score c	Workers living 20–30 km from the explosion site and who were neither employees in the industrial area nor clean-up workers	Controls	0		
Tjalvin, G., et al. 2015	Chemical accident	Subj	Obj	Neurological complaints score c	Workers at the time of the explosion and/or clean-up workers	Exposed	1,86	1,04	2,69
Tjalvin, G., et al. 2017	Chemical accident	Subj	Subj	Total SHC score d	Odour score	Low odour score	0		
Tjalvin, G., et al. 2017	Chemical accident	Subj	Subj	Total SHC score d	Odour score	High odour score	3,7	2,03	5,37
Tjalvin, G., et al. 2017	Chemical accident	Subj	Subj	Neurological complaints score c	Odour score	Low odour score	0		
Tjalvin, G., et al. 2017	Chemical accident	Subj	Subj	Neurological complaints score c	Odour score	High odour score	1,02	0,56	1,49

c Neurological complaints score: Extra heartbeats, Hot flushes, Sleep problems, Tiredness, Dizziness, Anxiety and Sadness/Depression experienced past month

d SHC (Subjective Health Complaints Inventory)

Appendix S11. Nausea and vomiting

NAUSEA/VOMITING: 14 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Nausea past 2 years	log e (NH3 exposure)	-0,05	-0,82	0,72
Schinasi 2011	AFO	Subj	Subj	Nausea previous 12 hours	Any odour in previous 12 hours (9-point scale)	0,21	-0,12	0,54
Steinheider 1998 (Nörvenich study)	AFO	Subj	Obj	Vomiting (7-point scale)	log (odour frequency from observation panel)	0,30	0,10	0,50
Steinheider 1998 (Nörvenich study)	AFO	Subj	Obj	Nausea (7-point scale)	log (odour frequency from observation panel)	0,51	0,24	0,78
Steinheider 1998 (Nörvenich study)	AFO	Subj	Obj	Retching (7-point scale)	log (odour frequency from observation panel)	0,36	0,14	0,58

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Nausea in the last 2 years	Odour annoyance	Not annoyed	1		
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Nausea in the last 2 years	Odour annoyance	Slightly annoyed	0,71	0,19	2,59
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Nausea in the last 2 years	Odour annoyance	Moderately annoyed	2,82	0,59	13,5
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Nausea in the last 2 years	Odour annoyance	Very or extremely annoyed	4,02	0,78	20,8

Appendix S11. Nausea and vomiting, Continued

NAUSEA/VOMITING: 14 studies									
GENERAL POPULATION: ADULTS									
Effect size was reported as an odds ratio (OR)									
Study	**Source**	**Type of outcome**	**Type of exposure**	**Outcome variable**	**Exposure variable**	**Subcategory**	**Value**	**95% CI inf**	**95% CI sup**
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Nausea in the last 2 years	NH3 exposure, µg/m3	<2	1		
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Nausea in the last 2 years	NH3 exposure, µg/m3	2–3	0,25	0,05	1,27
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Nausea in the last 2 years	NH3 exposure, µg/m3	>3	1,1	0,32	3,79
Segala 2003	Wastewater treatment	Subj	Obj	Nausea past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Nausea past 12 months	Distance (km)	1.5-3	0,88	0,58	1,34
Segala 2003	Wastewater treatment	Subj	Obj	Nausea past 12 months	Distance (km)	<1.5	0,88	0,54	1,42
Segala 2003	Wastewater treatment	Subj	Subj	Nausea past 12 months	Odour tolerance	Tolerant	1		
Segala 2003	Wastewater treatment	Subj	Subj	Nausea past 12 months	Odour tolerance	Moderately tolerant	1,81	1,21	2,72
Segala 2003	Wastewater treatment	Subj	Subj	Nausea past 12 months	Odour tolerance	Intolerant	3,52	2,14	5,8
Segala 2003	Wastewater treatment	Subj	Subj	Nausea past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Nausea past 12 months	Odour perception	Complaints with no impact in health	1,44	0,89	2,32
Segala 2003	Wastewater treatment	Subj	Subj	Nausea past 12 months	Odour perception	Complaints with impacts on health	2,11	1,13	3,94

Appendix S11. Nausea and vomiting, Continued

NAUSEA/VOMITING: 14 studies GENERAL POPULATION: ADULTS Effect size was reported as an odds ratio (OR)									
Study	**Source**	**Type of outcome**	**Type of exposure**	**Outcome variable**	**Exposure variable**	**Subcategory**	**Value**	**95% CI inf**	**95% CI sup**
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Nausea past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Nausea past 12 months	Distance (km)	1.5-3	1,2	0,7	2,1
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Nausea past 12 months	Distance (km)	<1.5	1,3	0,8	2
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Nausea past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011°	Waste treatment + composting	Subj	Subj	Nausea past 12 months	Odour perception	Yes	1,1	0,8	1,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Nausea past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011°	Waste treatment + composting	Subj	Subj	Nausea past 12 months	Odour annoyance	Yes	0,9	0,6	1,4
Heaney 2011	Landfill	Subj	Subj	Nausea previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011°	Landfill	Subj	Subj	Nausea previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	2,7	0,5	14,2
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nausea last 6 months	Reported odour of liquid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nausea last 6 months	Reported odour of liquid sewage treatment	None or faint	0,85	0,51	1,42
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nausea last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/very strong	1,39	0,79	2,45
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nausea last 6 months	Reported odour of solid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nausea last 6 months	Reported odour of solid sewage treatment	None or faint	1,49	0,79	2,82
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nausea last 6 months	Reported odour of solid sewage treatment	Moderate/strong/very strong	1,77	0,96	3,26
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nausea last 6 months	Reported livestock odour	None or faint	1		

Appendix S11. Nausea and vomiting, Continued

NAUSEA/VOMITING: 14 studies GENERAL POPULATION: ADULTS									
Effect size was reported as an odds ratio (OR)									
Study	**Source**	**Type of outcome**	**Type of exposure**	**Outcome variable**	**Exposure variable**	**Subcategory**	**Value**	**95% CI inf**	**95% CI sup**
Wing 2014°	Sewage treatment and AFO	Subj	Subj	Nausea last 6 months	Reported livestock odour	Moderate/strong/very strong	1,04	0,69	1,55
Shustermann 1991	Multiple sites (petrochemical, landfill, sewage treatment, rubber industry)	Subj	Subj	Nausea	Odour perception	No	1		
Shustermann 1991°	Multiple sites (petrochemical, landfill, sewage treatment, rubber industry)	Subj	Subj	Nausea	Odour perception	Yes	5,2	2,9	9,4
Herr 2009	Composting site	Subj	Obj	Nausea past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009°	Composting site	Subj	Obj	Nausea past 2 years	Residents near composting site	EnvExp-2	1,84	1,06	3,22
Herr 2009	Composting site	Subj	Obj	Vomiting past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009°	Composting site	Subj	Obj	Vomiting past 2 years	Residents near composting site	EnvExp-2	1,06	0,53	2,11
Lipscomb 1991	Hazardous waste site	Subj	Obj	Nausea past 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991°	Hazardous waste site	Subj	Obj	Nausea past 12 months	Odour zones from previous odour survey	High exposed	4,92	1,9	12,77
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Nauseous	Odour annoyance	No	1		
Hooiveld, M., et al. 2015°	AFO	Subj	Subj	Nauseous	Odour annoyance	Yes	1,2	0,74	1,97

° *Included in the meta-analysis*

Appendix S11. Nausea and vomiting, Continued

NAUSEA/VOMITING: 14 studies						
GENERAL POPULATION: ADULTS						
No association estimate in the study						
Study	**Source**	**Type of outcome**	**Type of exposure**	**Outcome variable**	**Exposure variable**	**Main results**
Kret, J., et al. 2018	Landfill	Subj	Obj	Nausea past 12 months	Distance (km)	No differences between landfill households and control households
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	Nausea, vomiting^	Odour annoyance/distance (3 areas)/olfactometry	No differences between areas
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Nausea, vomiting^	Distance (3 areas)	No differences between areas
Steinheider 1998 (Nettetal study)	Fertilizer manufacturing plant	Subj	Obj	Vomiting	Distance from the odour source/ Degree of annoyance	Higher frequency with increasing proximity to the source
Steinheider 1998 (Nettetal study)	Fertilizer manufacturing plant	Subj	Obj	Nausea	Distance from the odour source/ Degree of annoyance	Higher frequency with increasing proximity to the source
Steinheider 1998 (Nettetal study)	Fertilizer manufacturing plant	Subj	Obj	Retching	Distance from the odour source/ Degree of annoyance	Higher frequency with increasing proximity to the source

^ *included also dizziness*

Appendix S12. Regurgitation, reflux and gastric acid

RIGURGITATION/REFLUX/GASTRIC ACID: 2 studies
GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Reflux/gastric acid last month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Reflux/gastric acid last month	Odour annoyance	Yes	1,25	0,82	1,9
Herr 2009	Composting site	Subj	Obj	Regurgitation past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Regurgitation past 2 years	Residents near composting site	EnvExp-2	1,2	0,67	2,14

Appendix S13. Constipation

CONSTIPATION: 3 studies
GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Hooiveld, M., et al. 2015	Animal feeding operations	Subj	Subj	Obstipation	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	Animal feeding operations	Subj	Subj	Obstipation	Odour annoyance	Yes	2,04	1,26	3,31

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Main results
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Constipation	Distance (3 areas)	No differences between areas
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	Constipation	Odour annoyance/distance (3 areas)/olfactometry	Significant difference between areas in the expected direction among women

Appendix S14. Loss of appetite and intolerance of food

LOSS OF APPETITE, INTOLERANCE OF FOOD: 5 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Subj	Subj	poor appetite	Any odour in previous 12 hours (9-point scale)	-0,03	-0,5984	0,5384
Steinheider 1998	AFO	Subj	Obj	loss appetite score	log (odour frequency from observation panel)	0,665	0,34748	0,98252

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Heaney 2011	Landfill	Subj	Subj	Loss appetite previous 12 hours	Any odour in previous 12-hr	No	1		
Heaney 2011	Landfill	Subj	Subj	Loss appetite previous 12 hours	Any odour in previous 12-hr	Yes	0,7	0,2	2,2
Herr 2009	Composting site	Subj	Obj	Food intolerance past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Food intolerance past 2 years	Residents near composting site	EnvExp-2	1,69	0,89	3,2
Lipscomb 1991	Hazardous waste site	Subj	Obj	Loss appetite past 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991	Hazardous waste site	Subj	Obj	Loss appetite past 12 months	Odour zones from previous odour survey	High exposed	4,27	1,43	12,73

Appendix S15. Stomach discomfort, abdominal pain and bloating

STOMACH DISCOMFORT/COMPLAINTS, ABDOMINAL PAIN, GASTROINTESTINAL COMPLAINTS, BLOATING: 6 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Steinheider 1998 (Nörvenich study)	AFO	Subj	Obj	Stomach discomfort (7-point scale)	log (odour frequency from observation panel)	0,479	0,14188	0,81612

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Wing 2014	Sewage treatment and AFO	Subj	Subj	Abdominal pain last 6 months	Reported odour of liquid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Abdominal pain last 6 months	Reported odour of liquid sewage treatment	None or faint	0,85	0,51	1,42
Wing 2014	Sewage treatment and AFO	Subj	Subj	Abdominal pain last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/ very strong	1,39	0,79	2,45
Wing 2014	Sewage treatment and AFO	Subj	Subj	Abdominal pain last 6 months	Reported odour of solid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Abdominal pain last 6 months	Reported odour of solid sewage treatment	None or faint	1,49	0,79	2,82
Wing 2014	Sewage treatment and AFO	Subj	Subj	Abdominal pain last 6 months	Reported odour of solid sewage treatment	Moderate/strong/ very strong	1,77	0,96	3,26
Wing 2014	Sewage treatment and AFO	Subj	Subj	Abdominal pain last 6 months	Reported livestock odour	None or faint	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Abdominal pain last 6 months	Reported livestock odour	Moderate/strong/ very strong	1,04	0,69	1,55

Appendix S15. Stomach discomfort, abdominal pain and bloating, Continued

STOMACH DISCOMFORT/COMPLAINTS, ABDOMINAL PAIN, GASTROINTESTINAL COMPLAINTS, BLOATING: 6 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Wing 2014	Sewage treatment and AFO	Subj	Subj	Gastrointestinal symptoms (score) last 6 months	Reported odour of liquid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Gastrointestinal symptoms (score) last 6 months	Reported odour of liquid sewage treatment	None or faint	1,04	0,81	1,31
Wing 2014	Sewage treatment and AFO	Subj	Subj	Gastrointestinal symptoms (score) last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/ very strong	1,16	0,8	1,68
Wing 2014	Sewage treatment and AFO	Subj	Subj	Gastrointestinal symptoms (score) last 6 months	Reported odour of solid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Gastrointestinal symptoms (score) last 6 months	Reported odour of solid sewage treatment	None or faint	1,08	0,77	1,52
Wing 2014	Sewage treatment and AFO	Subj	Subj	Gastrointestinal symptoms (score) last 6 months	Reported odour of solid sewage treatment	Moderate/strong/ very strong	1,2	0,86	1,66
Wing 2014	Sewage treatment and AFO	Subj	Subj	Gastrointestinal symptoms (score) last 6 months	Reported livestock odour	None or faint	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Gastrointestinal symptoms (score) last 6 months	Reported livestock odour	Moderate/strong/ very strong	1,04	0,83	1,28
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Gastrointestinal symptoms last month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Gastrointestinal symptoms last month	Odour annoyance	Yes	1,37	1,16	1,6
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Stomach complaints last month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Stomach complaints last month	Odour annoyance	Yes	1,56	0,98	2,48
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Stomach pain last month	Odour annoyance	No	1		

Appendix S15. Stomach discomfort, abdominal pain and bloating, Continued

STOMACH DISCOMFORT/COMPLAINTS, ABDOMINAL PAIN, GASTROINTESTINAL COMPLAINTS, BLOATING: 6 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Stomach pain last month	Odour annoyance	Yes	1,73	1,11	2,79
Heaney 2011	Landfill	Subj	Subj	Any gastrointestinal (diarrhoea, nausea or vomiting, loss of appetite)	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Any gastrointestinal (diarrhoea, nausea or vomiting, loss of appetite)	Any odour in previous 12 hours (5-point Likert scale)	Yes	1	0,4	2,6
Herr 2009	Composting site	Subj	Obj	Bloating past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Bloating past 2 years	Residents near composting site	EnvExp-2	1,09	0,65	1,84
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Stomach pain past 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Stomach pain past 12 months	Odour zones from previous odour survey	High exposed	1,68	0,81	3,47

** Unadjusted models*

Appendix S15. Stomach discomfort, abdominal pain and bloating, Continued

STOMACH DISCOMFORT/COMPLAINTS, ABDOMINAL PAIN, GASTROINTESTINAL COMPLAINTS, BLOATING: 6 studies WORKERS									
Effect reported as mean difference between groups									
Study	**Source**	**Type of outcome**	**Type of exposure**	**Outcome variable**	**Exposure variable**	**Subcategory**	**Value**	**95% CI inf**	**95% CI sup**
Tjalvin, G., et al. 2015	Chemical accident	Subjective	Objective	Gastrointestinal complaints score*	Workers living 20–30 km from the explosion site and who were neither employees in the industrial area nor clean-up workers	Control	0		
Tjalvin, G., et al. 2015	Chemical accident	Subjective	Objective	Gastrointestinal complaints score*	Workers at the time of the explosion and/or clean-up workers	Exposed	0,47	-0.28	1,22

** Gastrointestinal symptoms score: Heartburn, Stomach discomfort, Ulcer/Non-ulcer dyspepsia, Stomach pain, Gas discomfort, Diarrhoea and Constipation experienced past month*

Appendix S16. Disgust, bad taste in mouth and coated tongue

DISGUST, BAD TASTE IN MOUTH/COATED TONGUE: 2 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Steinheider 1998 (Nörvenich study)	AFO	Subj	Obj	Disgust (7-point scale)	log (odour frequency from observation panel)	0,583	0,29684	0,86916

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Herr 2009	Composting site	Subj	Obj	Bad taste in mouth, or excessively coated tongue past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Bad taste in mouth, or excessively coated tongue past 2 years	Residents near composting site	EnvExp-2	1,19	0,61	2,33

Appendix S17. Diarrhoea

DIARRHOEA: 7 studies									
GENERAL POPULATION: ADULTS									
Effect size reported as a regression coefficient (β) for unit increase compared to reference									
Study	**Source**	**Type of outcome**	**Type of exposure**	**Outcome variable**	**Exposure variable**		**Value**	**95% CI inf**	**95% CI sup**
Schinasi 2011	AFO	Subj	Subj	Diarrhoea previous 12 hours	Any odour in previous 12 hours (9-point scale)		-0,1	-0,6488	0,4488
Effect size was reported as an odds ratio (OR)									
Study	**Source**	**Type of outcome**	**Type of exposure**	**Outcome variable**	**Exposure variable**	**Subcategory**	**Value**	**95% CI inf**	**95% CI sup**
Segala 2003	Wastewater treatment	Subj	Obj	Diarrhoea past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Diarrhoea past 12 months	Distance (km)	1.5-3	0,71	0,51	1
Segala 2003	Wastewater treatment	Subj	Obj	Diarrhoea past 12 months	Distance (km)	<1.5	0,93	0,65	1,33
Segala 2003	Wastewater treatment	Subj	Subj	Diarrhoea past 12 months	Odour tolerance	Tolerant	1		
Segala 2003	Wastewater treatment	Subj	Subj	Diarrhoea past 12 months	Odour tolerance	Moderately tolerant	1,45	1,07	1,96
Segala 2003	Wastewater treatment	Subj	Subj	Diarrhoea past 12 months	Odour tolerance	Intolerant	2,18	1,43	3,33
Segala 2003	Wastewater treatment	Subj	Subj	Diarrhoea past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Diarrhoea past 12 months	Odour perception	Complaints with no impact in health	1,08	0,74	1,58
Segala 2003	Wastewater treatment	Subj	Subj	Diarrhoea past 12 months	Odour perception	Complaints with impacts on health	2,83	1,82	4,4
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Diarrhoea last month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Diarrhoea last month	Odour annoyance	Yes	1,46	0,97	2,21

Appendix S17. Diarrhoea, Continued

DIARRHOEA: 7 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Diarrhoea past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Diarrhoea past 12 months	Distance (km)	1.5-3	1,1	0,7	1,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Diarrhoea past 12 months	Distance (km)	<1.5	1,1	0,8	1,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Diarrhoea past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Diarrhoea past 12 months	Odour perception	Yes	1,3	1	1,7
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Diarrhoea past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Diarrhoea past 12 months	Odour annoyance	Yes	1,2	0,9	1,7
Heaney 2011	Landfill	Subj	Subj	Diarrhoea previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Diarrhoea previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	2,6	0,2	29,5
Herr 2009	Composting site	Subj	Obj	Frequent diarrhoea past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Frequent diarrhoea past 2 years	Residents near composting site	EnvExp-2	0,97	0,38	2,46
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Diarrhoea past 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Diarrhoea past 12 months	Odour zones from previous odour survey	High exposed	1,7	0,78	3,68

** Unadjusted models*

Appendix S18. Cough and phlegm

COUGH/PHLEGM: 11 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Subj	Subj	Cough after 10 minutes outdoor	Any odour in previous 12 hours (9-point scale)	0,25	0,11	0,39
Schinasi 2011	AFO	Subj	Subj	Cough previous 12 hours	Any odour in previous 12 hours (9-point scale)	0,36	0,07	0,65
Schinasi 2011	AFO	Subj	Subj	phlegm previous 12 hours	Any odour in previous 12 hours (9-point scale)	0,19	-0,08	0,46
Steinheider 1998 (Nörvenich study)	AFO	Subj	Obj	Cough (7-point scale)	log (odour frequency from observation panel)	0,37	0,03	0,70

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Cough past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Cough past 12 months	Distance (km)	1.5-3	1,3	0,9	2
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Cough past 12 months	Distance (km)	<1.5	1,3	1	1,8
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Cough past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011°	Waste treatment + composting	Subj	Subj	Cough past 12 months	Odour perception	Yes	1,1	0,8	1,4
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Cough past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011°	Waste treatment + composting	Subj	Subj	Cough past 12 months	Odour annoyance	Yes	1,1	0,8	1,5
Baldacci, S., et al. 2015	Waste incinerator	Subj	Subj	Phlegm	Odour annoyance	No	1		
Baldacci, S., et al. 2015°	Waste incinerator	Subj	Subj	Phlegm	Odour annoyance	Yes	2,1	1,4	3,2
Baldacci, S., et al. 2015	Waste incinerator	Subj	Subj	Cough	Odour annoyance	No	1		
Baldacci, S., et al. 2015°	Waste incinerator	Subj	Subj	Cough	Odour annoyance	Yes	2,5	1,74	3,7

Appendix S18. Cough and phlegm, Continued

COUGH/PHLEGM: 11 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Segala 2003	Wastewater treatment	Subj	Obj	Cough past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Cough past 12 months	Distance (km)	1.5-3	1	0,81	1,2
Segala 2003	Wastewater treatment	Subj	Obj	Cough past 12 months	Distance (km)	<1.5	1	0,77	1,2
Segala 2003	Wastewater treatment	Subj	Subj	Cough past 12 months	Odour tolerance	Tolerant	1		
Segala 2003	Wastewater treatment	Subj	Subj	Cough past 12 months	Odour tolerance	Moderately tolerant	1,5	1,23	1,8
Segala 2003	Wastewater treatment	Subj	Subj	Cough past 12 months	Odour tolerance	Intolerant	2,4	1,75	3,2
Segala 2003	Wastewater treatment	Subj	Subj	Cough past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Cough past 12 months	Odour perception	Complaints but sense impact in health	1,4	1,13	1,8
Segala 2003	Wastewater treatment	Subj	Subj	Cough past 12 months	Odour perception	Complaints with impacts on health	1,6	1,15	2,3
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Cough in last month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015°	AFO	Subj	Subj	Cough in last month	Odour annoyance	Yes	1,3	0,93	1,9
Heaney 2011	Landfill	Subj	Subj	Cough previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011°	Landfill	Subj	Subj	Cough previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	2	1	3,9
Wing 2014	Sewage treatment and CAFO	Subj	Subj	Cough last 6 months	Reported odour of liquid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and CAFO	Subj	Subj	Cough last 6 months	Reported odour of liquid sewage treatment	None or faint	1	0,72	1,3
Wing 2014	Sewage treatment and CAFO	Subj	Subj	Cough last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/very strong	1,1	0,73	1,5

Appendix S18. Cough and phlegm, Continued

COUGH/PHLEGM: 11 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Wing 2014	Sewage treatment and AFO	Subj	Subj	Cough last 6 months	Reported odour of solid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Cough last 6 months	Reported odour of solid sewage treatment	None or faint	1,2	0,78	1,8
Wing 2014	Sewage treatment and AFO	Subj	Subj	Cough last 6 months	Reported odour of solid sewage treatment	Moderate/strong/very strong	0,9	0,54	1,5
Wing 2014	Sewage treatment and AFO	Subj	Subj	Cough last 6 months	Reported livestock odour	None or faint	1		
Wing 2014°	Sewage treatment and AFO	Subj	Subj	Cough last 6 months	Reported livestock odour	Moderate/strong/very strong	1,3	1,01	1,7

° *Included in the meta-analysis*

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Main results
Kret, J., et al. 2018	Landfill	Subj	Obj	Cough past 12 months	Distance (km)	No difference between landfill households and control households
Steinheider 1998 (Nettetal study)	AFO	Subj	Obj	Cough	Distance from the odour source/ Degree of annoyance	Higher frequency in proximity to the odour source
Deane and Sanders 1977	Paper plant	Subj	Obj	Cough grade 1 or 2	Distance (3 areas)	No difference between areas I, II and III
Deane and Sanders 1977	Paper plant	Subj	Sub	Cough grade 1 or 2	Odour annoyance	No difference between very much/moderately bothered and little or not bothered
Deane and Sanders 1977	Paper plant	Subj	Obj	Phlegm grade 1 or 2	Distance (3 areas)	Higher prevalence in area I than area III
Deane and Sanders 1977	Paper plant	Subj	Sub	Phlegm grade 1 or 2	Odour annoyance	No difference between very much/moderately bothered and little or not bothered
Deane and Sanders 1978	Paper plant	Subj	Obj	Cough grade 1 or 2	Distance (3 areas)	No difference between areas I, II and III in the expected direction
Deane and Sanders 1978	Paper plant	Subj	Obj	Phlegm grade 1 or 2	Distance (3 areas)	No difference between areas I, II and III

Appendix S19. Wheezing

WHEEZING: 8 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi et al. 2011	CAFO	Subj	Subj	Wheezing severity score previous 12 hours	Any odour in previous 12 hours (9-point scale)	0,18	-0,13	0,49

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Radon et al. 2007	AFO	Subj	Subj	Wheezing without cold past 12 months	Odour annoyance	Not at all	1		
Radon et al. 2007	AFO	Subj	Subj	Wheezing without cold past 12 months	Odour annoyance	Somewhat	1,2	0,9	1,7
Radon et al. 2007	AFO	Subj	Subj	Wheezing without cold past 12 months	Odour annoyance	Moderately	2,2	1,42	3,4
Radon et al. 2007	AFO	Subj	Subj	Wheezing without cold past 12 months	Odour annoyance	Strongly	3	1,8	4,9
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Wheezing past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Wheezing past 12 months	Odour perception	Yes	1,2	0,8	1,7
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Wheezing past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Wheezing past 12 months	Odour annoyance	Yes	1,1	0,7	1,7
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Wheezing past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Wheezing past 12 months	Distance (km)	1.5-3	1,5	0,8	2,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Wheezing past 12 months	Distance (km)	<1.5	1,4	0,9	2,4

Appendix S19. Wheezing, Continued

WHEEZING: 8 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Wing 2014	AFO + sewage treatment	Subj	Subj	Wheezing past 6 months	Livestock odour	Non-exposed area	1		
Wing 2014	AFO + sewage treatment	Subj	Subj	Wheezing past 6 months	Livestock odour	Moderate/strong/very strong	1,5	0,95	2,5
Wing 2014	AFO + sewage treatment	Subj	Subj	Wheezing past 6 months	Liquid sewage sludge odour	Non-exposed area	1		
Wing 2014	AFO + sewage treatment	Subj	Subj	Wheezing past 6 months	Liquid sewage sludge odour	None or faint	1,4	0,73	2,5
Wing 2014	AFO + sewage treatment	Subj	Subj	Wheezing past 6 months	Liquid sewage sludge odour	Moderate/strong/very strong	1,8	0,99	3,2
Wing 2014	AFO + sewage treatment	Subj	Subj	Wheezing past 6 months	Solid sewage sludge odour	Non-exposed area	1		
Wing 2014	AFO + sewage treatment	Subj	Subj	Wheezing past 6 months	Solid sewage sludge odour	None or faint	1,4	0,57	3,5
Wing 2014	AFO + sewage treatment	Subj	Subj	Wheezing past 6 months	Solid sewage sludge odour	Moderate/strong/very strong	1,5	0,72	3,3
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Wheezing past 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Wheezing past 12 months	Odour zones from previous odour survey	High exposed	4,3	1,43	13

** Unadjusted models*

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Main results
Kret, J., et al. 2018	Landfill	Subj	Obj	Wheezing past 12 months	Distance (km)	No difference between exposed and not exposed areas

Appendix S19. Wheezing, Continued

WHEEZING: 8 studies

ADOLESCENTS

Effect size was reported as an prevalence ratios (PRs)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Mirabelli 2006	AFO	Subj	Subj	Wheezing past 12 months (current wheeze)	Odour annoyance	None	1		
Mirabelli 2006	AFO	Subj	Subj	Wheezing past 12 months (current wheeze)	Odour annoyance	Outside school only	1	0,95	1,1
Mirabelli 2006	AFO	Subj	Subj	Wheezing past 12 months (current wheeze)	Odour annoyance	Outside + inside <2 times/mo	1	0,94	1,1
Mirabelli 2006	AFO	Subj	Subj	Wheezing past 12 months (current wheeze)	Odour annoyance	Outside + inside ≥2 times/mo	1,2	1,01	1,4
Mirabelli 2006	AFO	Subj	Subj	Current wheezing without physician diagnosis	Odour annoyance	No	1		
Mirabelli 2006	AFO	Subj	Subj	Current wheezing without physician diagnosis	Odour annoyance	Yes	1	0,96	1,1
Mirabelli 2006	AFO	Subj	Subj	Severe wheeze (among individuals with current wheeze)	Odour annoyance	No	1		
Mirabelli 2006	AFO	Subj	Subj	Severe wheeze (among individuals with current wheeze)	Odour annoyance	Yes	1,1	1	1,1
Mirabelli 2006	AFO	Subj	Subj	Frequent severe wheeze (among individuals with current wheeze)	Odour annoyance	No	1		
Mirabelli 2006	AFO	Subj	Subj	Frequent severe wheeze (among individuals with current wheeze)	Odour annoyance	Yes	1,1	0,98	1,1
Mirabelli 2006	AFO	Subj	Obj	Wheezing past 12 months (current wheeze)	Distance (miles) from nearest swine AFO	>3	1		
Mirabelli 2006	AFO	Subj	Obj	Wheezing past 12 months (current wheeze)	Distance (miles) from nearest swine AFO	≤3	1	0,99	1,1
Mirabelli 2006	AFO	Subj	Obj	Current wheezing without physician diagnosis	Distance (miles) from nearest swine AFO	>3	1		
Mirabelli 2006	AFO	Subj	Obj	Current wheezing without physician diagnosis	Distance (miles) from nearest swine AFO	≤3	1	0,98	1,1
Mirabelli 2006	AFO	Subj	Obj	Severe wheeze (among individuals with current wheeze)	Distance (miles) from nearest swine AFO	>3	1		
Mirabelli 2006	AFO	Subj	Obj	Severe wheeze (among individuals with current wheeze)	Distance (miles) from nearest swine AFO	≤3	1	0,97	1,1

Appendix S19. Wheezing, Continued

WHEEZING: 8 studies

ADOLESCENTS

Effect size was reported as an prevalence ratios (PRs)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Mirabelli 2006	AFO	Subj	Obj	Frequent severe wheeze (among individuals with current wheeze)	Distance (miles) from nearest swine AFO	>3	1		
Mirabelli 2006	AFO	Subj	Obj	Frequent severe wheeze (among individuals with current wheeze)	Distance (miles) from nearest swine AFO	≤3	1	0,92	1,1
Mirabelli 2006	AFO	Subj	Obj	Wheezing past 12 months (current wheeze)	Animal's mass weighted for distance	<1th tertiles	1		
Mirabelli 2006	AFO	Subj	Obj	Wheezing past 12 months (current wheeze)	Animal's mass weighted for distance	1-2 tertiles	1,1	1,01	1,2
Mirabelli 2006	AFO	Subj	Obj	Wheezing past 12 months (current wheeze)	Animal's mass weighted for distance	2-3 tertiles	1	0,96	1,1
Mirabelli 2006	AFO	Subj	Obj	Wheezing past 12 months (current wheeze)	Animal's mass weighted for distance	>3 tertiles	1	0,92	1,1

Appendix S20. Asthma

ASTHMA: 6 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Asthma diagnosed by physician	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Asthma diagnosed by physician	Distance (km)	1.5-3	1,4	0,7	2,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Asthma diagnosed by physician	Distance (km)	<1.5	1,3	0,7	2,2
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Asthma diagnosed by physician	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Asthma diagnosed by physician	Odour perception	Yes	0,9	0,6	1,4
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Asthma diagnosed by physician	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Asthma diagnosed by physician	Odour annoyance	Yes	0,8	0,5	1,3
Baldacci, S., et al. 2015	Waste incinerator	Subj	Subj	Asthma diagnosis	Odour annoyance	No	1		
Baldacci, S., et al. 2015	Waste incinerator	Subj	Subj	Asthma diagnosis	Odour annoyance	Yes	2	1,14	3,4
Baldacci, S., et al. 2015	Waste incinerator	Subj	Subj	Asthma symptoms	Odour annoyance	No	1		
Baldacci, S., et al. 2015	Waste incinerator	Subj	Subj	Asthma symptoms	Odour annoyance	Yes	1,9	1,23	2,8
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Asthma symptoms last month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Asthma symptoms last month	Odour annoyance	Yes	1	0,8	1,2

Appendix S20. Asthma, Continued

ASTHMA: 6 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Segala 2003	Wastewater treatment	Subj	Obj	Asthma symptoms past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Asthma symptoms past 12 months	Distance (km)	1.5-3	1	0,65	1,5
Segala 2003	Wastewater treatment	Subj	Obj	Asthma symptoms past 12 months	Distance (km)	<1.5	0,8	0,51	1,3
Segala 2003	Wastewater treatment	Subj	Subj	Asthma symptoms past 12 months	Odour tolerance	Tolerant	1		
Segala 2003	Wastewater treatment	Subj	Subj	Asthma symptoms past 12 months	Odour tolerance	Moderately tolerant	2,6	1,68	4,1
Segala 2003	Wastewater treatment	Subj	Subj	Asthma symptoms past 12 months	Odour tolerance	Intolerant	7,9	4,88	13
Segala 2003	Wastewater treatment	Subj	Subj	Asthma symptoms past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Asthma symptoms past 12 months	Odour perception	Complaints with no impact in health	1	0,63	1,6
Segala 2003	Wastewater treatment	Subj	Subj	Asthma symptoms past 12 months	Odour perception	Complaints with impacts on health	1,4	0,75	2,6
Radon 2007	AFO	Subj	Subj	Asthma diagnosed by physician	Odour annoyance	Not at all	1		
Radon 2007	AFO	Subj	Subj	Asthma diagnosed by physician	Odour annoyance	Somewhat	1,4	0,95	2,1
Radon 2007	AFO	Subj	Subj	Asthma diagnosed by physician	Odour annoyance	Moderately	1,5	0,84	2,7
Radon 2007	AFO	Subj	Subj	Asthma diagnosed by physician	Odour annoyance	Strongly	2,5	1,32	4,8

GENERAL POPULATION: ADOLESCENTS

Effect size was reported as a prevalence ratio (PR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Mirabelli 2006	AFO	Subj	Subj	Physician-diagnosed asthma	Odour annoyance	No reported odour	1		
Mirabelli 2006	AFO	Subj	Subj	Physician-diagnosed asthma	Odour annoyance	Odour reported outside or inside school building	1	0,95	1,1

Appendix S20. Asthma, Continued

ASTHMA: 6 studies

GENERAL POPULATION: ADOLESCENTS

Effect size was reported as a prevalence ratio (PR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Mirabelli 2006	AFO	Subj	Subj	Asthma-related physician visit, emergency visit, and/or hospitalization in past year	Odour annoyance	No reported odour	1		
Mirabelli 2006	AFO	Subj	Subj	Asthma-related physician visit, emergency visit, and/or hospitalization in past year	Odour annoyance	Odour reported outside or inside school building	1	0,95	1,1
Mirabelli 2006	AFO	Subj	Subj	Asthma medication use in past year	Odour annoyance	No reported odour	1		
Mirabelli 2006	AFO	Subj	Subj	Asthma medication use in past year	Odour annoyance	Odour reported outside or inside school building	1	0,96	1,1
Mirabelli 2006	AFO	Subj	Obj	Physician-diagnosed asthma	Distance (miles) from nearest swine CAFO	>3	1		
Mirabelli 2006	AFO	Subj	Obj	Physician-diagnosed asthma	Distance (miles) from nearest swine CAFO	≤3	1,1	1,01	1,1
Mirabelli 2006	AFO	Subj	Obj	Asthma-related physician visit, emergency visit, and/or hospitalization in past year	Distance (miles) from nearest swine CAFO	>3	1		
Mirabelli 2006	AFO	Subj	Obj	Asthma-related physician visit, emergency visit, and/or hospitalization in past year	Distance (miles) from nearest swine CAFO	≤3	1,1	1	1,1
Mirabelli 2006	AFO	Subj	Obj	Asthma medication use in past year	Distance (miles) from nearest swine CAFO	>3	1		
Mirabelli 2006	AFO	Subj	Obj	Asthma medication use in past year	Distance (miles) from nearest swine CAFO	≤3	1,1	1	1,2
Mirabelli 2006	AFO	Subj	Subj	Missed school in past year as a result of asthma symptoms	Odour annoyance	No reported odour	1		
Mirabelli 2006	AFO	Subj	Subj	Missed school in past year as a result of asthma symptoms	Odour annoyance	Odour reported outside or inside school building	1	0,94	1,1
Mirabelli 2006	AFO	Subj	Obj	Missed school in past year as a result of asthma symptoms	Distance (miles) from nearest swine CAFO	>3	1		

Appendix S20. Asthma, Continued

ASTHMA: 6 studies

GENERAL POPULATION: ADOLESCENTS

Effect size was reported as a prevalence ratio (PR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Mirabelli 2006	AFO	Subj	Obj	Missed school in past year as a result of asthma symptoms	Distance (miles) from nearest swine CAFO	≤3	1,1	0,98	1,1
Mirabelli 2006	AFO	Subj	Subj	Asthma-related activity limitations	Odour annoyance	No reported odour	1		
Mirabelli 2006	AFO	Subj	Subj	Asthma-related activity limitations	Odour annoyance	Odour reported outside or inside school building	1,1	1,01	1,2
Mirabelli 2006	AFO	Subj	Obj	Asthma-related activity limitations	Distance (miles) from nearest swine CAFO	>3	1		
Mirabelli 2006	AFO	Subj	Obj	Asthma-related activity limitations	Distance (miles) from nearest swine CAFO	≤3	1	0,96	1,1

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Main results
Kret, J., et al. 2018	Landfill	Subj	Obj	Asthma diagnosed less that 6 years ago	Distance (km)	No difference between exposed and not exposed areas
Kret, J., et al. 2018	Landfill	Subj	Obj	Asthma diagnosed 6-10 years ago	Distance (km)	No difference between exposed and not exposed areas
Kret, J., et al. 2018	Landfill	Subj	Obj	Asthma diagnosed over 10 years ago	Distance (km)	No difference between exposed and not exposed areas
Kret, J., et al. 2018	Landfill	Subj	Obj	Ever told have asthma	Distance (km)	No difference between exposed and not exposed areas
Kret, J., et al. 2018	Landfill	Subj	Obj	Asthma symptoms past 12 months	Distance (km)	No difference between exposed and not exposed areas

Appendix S21. Shortness of breath and dyspnea

SHORTNESS OF BREATH/DYSPNEA: 10 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Subj	Subj	Shortness of breath/difficulty breathing previous 12-hours	Any odour in previous 12 hours (9-point scale)	0,50	0,21	0,79
Steinheider 1998 (Nörvenich study)	AFO	Subj	Obj	Shortness of breath/difficulty breathing (7-point scale)	log (odour frequency from observation panel)	0,35	0,09	0,61

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Shortness of breath past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Shortness of breath past 12 months	Distance (km)	1.5-3	1,5	0,8	2,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Shortness of breath past 12 months	Distance (km)	<1.5	1,5	0,9	2,4
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Shortness of breath past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Shortness of breath past 12 months	Odour perception	Yes	0,9	0,7	1,4
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Shortness of breath past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Shortness of breath past 12 months	Odour annoyance	Yes	1,5	1	2,2

Appendix S21. Shortness of breath and dyspnea, Continued

SHORTNESS OF BREATH/DYSPNEA: 10 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Baldacci, S., et al. 2015	waste incinerator	Subj	Subj	Dyspnoea past 12 months	Odour annoyance	No	1		
Baldacci, S., et al. 2015	waste incinerator	Subj	Subj	Dyspnoea past 12 months	Odour annoyance	Yes	1,9	1,33	2,7
Heaney 2011	Landfill	Subj	Subj	Shortness of breath previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Shortness of breath previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	1,9	0,9	4,2
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Shortness of breath/difficulty breathing in last month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Shortness of breath/difficulty breathing in last month	Odour annoyance	Yes	1,4	0,9	2,1
Wing 2014	Sewage treatment and AFO	Subj	Subj	Shortness of breath/difficulty breathing last 6 months	Reported odour of liquid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Shortness of breath/difficulty breathing last 6 months	Reported odour of liquid sewage treatment	None or faint	1,2	0,71	2
Wing 2014	Sewage treatment and AFO	Subj	Subj	Shortness of breath/difficulty breathing last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/very strong	1,1	0,58	2,1
Wing 2014	Sewage treatment and AFO	Subj	Subj	Shortness of breath/difficulty breathing last 6 months	Reported odour of solid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Shortness of breath/difficulty breathing last 6 months	Reported odour of solid sewage treatment	None or faint	1,4	0,69	2,9
Wing 2014	Sewage treatment and AFO	Subj	Subj	Shortness of breath/difficulty breathing last 6 months	Reported odour of solid sewage treatment	Moderate/strong/very strong	1,4	0,75	2,5

Appendix S21. Shortness of breath and dyspnea, Continued

SHORTNESS OF BREATH/DYSPNEA: 10 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Wing 2014	Sewage treatment and AFO	Subj	Subj	Shortness of breath/difficulty breathing last 6 months	Reported livestock odour	None or faint	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Shortness of breath/difficulty breathing last 6 months	Reported livestock odour	Moderate/strong/very strong	1,5	1,02	2,3

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Main results
Kret, J., et al. 2018	Landfill	Subj	Obj	Shortness of breath past 12 months	Distance (km)	Higher prevalence in landfill households than in control households
Steinheider 1998 (Nettetal study)	AFO	Subj	Obj	Difficulties breathing	Distance from the odour source (adjustment for odour annoyance)	Higher symptom-reporting with increasing distance from the odour source
Deane and Sanders 1977	Paper plant	Subj	Obj	Shortness of breath	Distance (3 areas)	No difference between areas I, II and III even stratifying by odour annoyance
Deane and Sanders 1977	Paper plant	Subj	Sub	Shortness of breath	Odour annoyance	Higher prevalence in very much/moderately bothered vs little or not bothered
Deane and Sanders 1978*	Petrochemical plants	Subj	Obj	Shortness of breath grade 2 or greater last 2 weeks	Distance (3 areas)	No difference between areas I, II and III
Deane and Sanders 1978*	Petrochemical plants	Subj	Obj	Shortness of breath grade 3 or greater last 2 weeks	Distance (3 areas)	Significant opposite area trend only among men

Appendix S22. Respiratory infection

RESPIRATORY INFECTIONS: 2 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Respiratory infection past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Respiratory infection past 12 months	Distance (km)	1.5-3	1,1	0,7	1,7
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Respiratory infection past 12 months	Distance (km)	<1.5	1	0,7	1,4
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Respiratory infection past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Respiratory infection past 12 months	Odour perception	Yes	1,1	0,8	1,4
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Respiratory infection past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Respiratory infection past 12 months	Odour annoyance	Yes	1,2	0,9	1,7
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Maxillary sinusitis/bronchitis/pneumonia past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Maxillary sinusitis/bronchitis/pneumonia past 12 months	Distance (km)	1.5-3	0,8	0,5	1,3
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Maxillary sinusitis/bronchitis/pneumonia past 12 months	Distance (km)	<1.5	0,9	0,6	1,3
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Maxillary sinusitis/bronchitis/pneumonia past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Maxillary sinusitis/bronchitis/pneumonia past 12 months	Odour perception	Yes	0,9	0,7	1,3

Appendix S22. Respiratory infection, Continued

RESPIRATORY INFECTIONS: 2 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Maxillary sinusitis/bronchitis/pneumonia past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Maxillary sinusitis/bronchitis/pneumonia past 12 months	Odour annoyance	Yes	1,1	0,7	1,6
Segala 2003	Wastewater treatment	Subj	Obj	Respiratory infection past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Respiratory infection past 12 months	Distance (km)	1.5-3	0,7	0,51	1
Segala 2003	Wastewater treatment	Subj	Obj	Respiratory infection past 12 months	Distance (km)	<1.5	0,8	0,54	1,1
Segala 2003	Wastewater treatment	Subj	Subj	Respiratory infection past 12 months	Odour tolerance	Tolerant	1		
Segala 2003	Wastewater treatment	Subj	Subj	Respiratory infection past 12 months	Odour tolerance	Moderately tolerant	1,8	1,25	2,4
Segala 2003	Wastewater treatment	Subj	Subj	Respiratory infection past 12 months	Odour tolerance	Intolerant	4,8	3,24	7,1
Segala 2003	Wastewater treatment	Subj	Subj	Respiratory infection past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Respiratory infection past 12 months	Odour perception	Complaints but sense impact in health	1	0,67	1,5
Segala 2003	Wastewater treatment	Subj	Subj	Respiratory infection past 12 months	Odour perception	Complaints with impacts on health	1,4	0,83	2,4

Appendix S23. COPD

COPD: 3 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Baldacci, S., et al. 2015	Waste incinerator	Subj	Subj	COPD symptoms	Odour annoyance	No	1		
Baldacci, S., et al. 2015	Waste incinerator	Subj	Subj	COPD symptoms	Odour annoyance	Yes	1,9	1,01	3,5
Segala 2003	Wastewater treatment	Subj	Obj	COPD symptoms past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	COPD symptoms past 12 months	Distance (km)	1.5-3	0,7	0,48	1,1
Segala 2003	Wastewater treatment	Subj	Obj	COPD symptoms past 12 months	Distance (km)	<1.5	0,8	0,53	1,2
Segala 2003	Wastewater treatment	Subj	Subj	COPD symptoms past 12 months	Odour tolerance	Tolerant	1		
Segala 2003	Wastewater treatment	Subj	Subj	COPD symptoms past 12 months	Odour tolerance	Moderately tolerant	1,9	1,32	2,7
Segala 2003	Wastewater treatment	Subj	Subj	COPD symptoms past 12 months	Odour tolerance	Intolerant	3	1,84	4,7
Segala 2003	Wastewater treatment	Subj	Subj	COPD symptoms past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	COPD symptoms past 12 months	Odour perception	Complaints but sense impact in health	1,1	0,72	1,7
Segala 2003	Wastewater treatment	Subj	Subj	COPD symptoms past 12 months	Odour perception	Complaints with impacts on health	2,1	1,21	3,5

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Main results
Kret, J., et al. 2018	Landfill	Subj	Obj	COPD diagnosed less than 6 years ago	Distance (km)	No difference between landfill households and control households
Kret, J., et al. 2018	Landfill	Subj	Obj	COPD diagnosed 6-10 years ago	Distance (km)	No difference between landfill households and control households
Kret, J., et al. 2018	Landfill	Subj	Obj	COPD diagnosed over 10 years ago	Distance (km)	No difference between landfill households and control households
Kret, J., et al. 2018	Landfill	Subj	Obj	Ever told have COPD	Distance (km)	No difference between landfill households and control households

Appendix S24. Bronchial Obstruction Test

BRONCHIAL OBSTRUCTION TEST: 1 study

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Radon 2007	AFO	Obj	Subj	Bronchial Hyperresponsiveness to Methacholine	Odour annoyance	Not at all	1		
Radon 2007	AFO	Obj	Subj	Bronchial Hyperresponsiveness to Methacholine	Odour annoyance	Somewhat	1,2	0,83	1,8
Radon 2007	AFO	Obj	Subj	Bronchial Hyperresponsiveness to Methacholine	Odour annoyance	Moderately	0,9	0,5	1,7
Radon 2007	AFO	Obj	Subj	Bronchial Hyperresponsiveness to Methacholine	Odour annoyance	Strongly	1,1	0,5	2,5

Appendix S25. Lung Function

LUNG FUNCTION: 2 studies

GENERAL POPULATION: ADULTS

Effect reported as mean difference between exposure and control category

Study	Source	Type of ıtcome	Type of posure	Outcome variable	Exposure variable		Value	95% CI inf	95% CI sup
Radon 2007	AFO	Obj	Subj	FEV1% Predicted	Odour annoyance	Not at all	0		
Radon 2007	AFO	Obj	Subj	FEV1% Predicted	Odour annoyance	Somewhat	-1,5	-4	1
Radon 2007	AFO	Obj	Subj	FEV1% Predicted	Odour annoyance	Moderately	0,2	-3,7	4,2
Radon 2007	AFO	Obj	Subj	FEV1% Predicted	Odour annoyance	Strongly	-0,1	-5,2	5

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of ıtcome	Type of posure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Obj	Subj	FEV1 (forced expiratory volume in the first cond) previous 12 hours	Any odour in previous 12 hours (9-point scale)	-0,5	-3,62	2,6
Schinasi 2011	AFO	Obj	Subj	PEF (peak expiratory flow rate) previous 12 hours	Any odour in previous 12 hours (9-point scale)	-0	-0,04	-0

Appendix S26. Pain and pressing feeling chest

PAIN/PRESSING FEELING CHEST:6 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Subj	Subj	Chest tightness	Any odour in previous 12 hours (9-point scale)	0,12	-0,12	0,36

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Pain/pressing feeling/tightness of the chest past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Pain/pressing feeling/tightness of the chest past 12 months	Distance (km)	1.5-3	1,3	0,8	2,2
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Pain/pressing feeling/tightness of the chest past 12 months	Distance (km)	<1.5	1,3	0,8	2
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Pain/pressing feeling/tightness of the chest past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Pain/pressing feeling/tightness of the chest past 12 months	Odour perception	Yes	1,1	0,8	1,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Pain/pressing feeling/tightness of the chest past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Pain/pressing feeling/tightness of the chest past 12 months	Odour annoyance	Yes	1,2	0,8	1,9
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Chest tightness past 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Chest tightness past 12 months	Odour zones from previous odour survey	High exposed	2,3	0,77	6,7
Herr 2009	Composting site	Subj	Obj	Chest pain past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Chest pain past 2 years	Residents near composting site	EnvExp-2	0,8	0,36	1,7

Appendix S26. Pain and pressing feeling chest, Continued

PAIN/PRESSING FEELING CHEST:6 studies

GENERAL POPULATION: ADULTS

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Main results
Deane and Sanders 1977	Paper plant	Subj	Obj	Chest pain	Distance (3 areas)	No difference between areas I, II and III
Deane and Sanders 1977	Paper plant	Subj	Sub	Chest pain	Odour annoyance	No difference between very much/moderately bothered and little or not bothered
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Chest pain (frequently or occasionally)	Distance (3 areas)	Significant area trend among males in the opposite direction hypothesized

** Unadjusted models*

Appendix S27. Other respiratory symptoms

OTHER RESPIRATORY SYMPTOMS: 3 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Respiratory symptoms last month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Respiratory symptoms last month	Odour annoyance	Yes	1,2	1,03	1,4

Effect reported as mean difference between exposure and control category

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable		Value	95% CI inf	95% CI sup
Wing 2014	Sewage treatment and AFO	Subj	Subj	Lower respiratory symptoms (score) last 6 months	Reported odour of liquid sewage treatment	None or faint	-0	-0,28	0,3
Wing 2014	Sewage treatment and AFO	Subj	Subj	Lower respiratory symptoms (score) last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/very strong	0,3	-0,1	0,7
Wing 2014	Sewage treatment and AFO	Subj	Subj	Lower respiratory symptoms (score) last 6 months	Reported odour of solid sewage treatment	None or faint	0,2	-0,17	0,6
Wing 2014	Sewage treatment and AFO	Subj	Subj	Lower respiratory symptoms (score) last 6 months	Reported odour of solid sewage treatment	Moderate/strong/very strong	-0,1	-0,37	0,2
Wing 2014	Sewage treatment and AFO	Subj	Subj	Lower respiratory symptoms (score) last 6 months	Reported livestock odour	Moderate/strong/very strong	0,3	0,05	0,5

Appendix S28. Cold and flu

COLD/FLU: 3 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Cold/flu in last month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Cold/flu in last month	Odour annoyance	Yes	1,38	0,97	1,99
Lipscomb 1991	Hazardous waste site	Subj	Obj	Cold past 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991	Hazardous waste site	Subj	Obj	Cold past 12 months	Odour zones from previous odour survey	High exposed	1,68	0,81	3,47

WORKERS

Effect reported as mean difference between groups

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Tjalvin, G., et al. 2015	Chemical accident	Subjective	Objective	Flu score (cold/flu and coughing)	Workers living 20–30 km from the explosion site and who were neither employees in the industrial area nor clean-up workers	Controls	0		
Tjalvin, G., et al. 2015	Chemical accident	Subjective	Objective	Flu score (cold/flu and coughing)	Workers at the time of the explosion and/or clean-up workers	Exposed	0,06	-0.40	0,51

Appendix S29. Non-allergic rhinitis, runny nose, blocked nose, itchy nose

NON-ALLERGIC RHINITIS, RUNNY, BLOCKED, ITCHY NOSE: 8 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Subj	Subj	Nasal irritation after 10 minutes outdoor	Any odour in previous 12 hours (9-point scale)	0,65	0,55	0,75
Schinasi 2011	AFO	Subj	Subj	Nasal irritation previous 12 hours	Any odour in previous 12 hours (9-point scale)	0,46	0,21	0,71
Schinasi 2011	AFO	Subj	Subj	Runny nose previous 12 hours	Any odour in previous 12 hours (9-point scale)	0,27	0,07	0,47

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Segala 2003	Wastewater treatment	Subj	Obj	Runny nose past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Runny nose past 12 months	Distance (km)	1.5-3	1,22	1,01	1,48
Segala 2003	Wastewater treatment	Subj	Obj	Runny nose past 12 months	Distance (km)	<1.5	1,02	0,83	1,25
Segala 2003	Wastewater treatment	Subj	Subj	Runny nose past 12 months	Odour tolerance	Tolerant	1		
Segala 2003	Wastewater treatment	Subj	Subj	Runny nose past 12 months	Odour tolerance	Moderately tolerant	1,66	1,4	1,98
Segala 2003	Wastewater treatment	Subj	Subj	Runny nose past 12 months	Odour tolerance	Intolerant	2,1	1,59	2,78
Segala 2003	Wastewater treatment	Subj	Subj	Runny nose past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Runny nose past 12 months	Odour perception	Complaints with no impact in health	1,25	1	1,55
Segala 2003	Wastewater treatment	Subj	Subj	Runny nose past 12 months	Odour perception	Complaints with impacts on health	1,69	1,22	2,32

Appendix S29. Non-allergic rhinitis, runny nose, blocked nose, itchy nose, Continued

NON-ALLERGIC RHINITIS, RUNNY, BLOCKED, ITCHY NOSE: 8 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Non-allergic rhinitis past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Non-allergic rhinitis past 12 months	Distance (km)	1.5-3	0,5	0,3	0,9
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Non-allergic rhinitis past 12 months	Distance (km)	<1.5	0,9	0,6	1,4
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Non-allergic rhinitis past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Non-allergic rhinitis past 12 months	Odour perception	Yes	1,1	0,8	1,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Non-allergic rhinitis past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Non-allergic rhinitis past 12 months	Odour annoyance	Yes	0,9	0,6	1,4
Heaney 2011	Landfill	Subj	Subj	Runny nose	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Runny nose	Any odour in previous 12 hours (5-point Likert scale)	Yes	2,6	1,4	4,9
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nasal congestion last 6 months	Reported odour of liquid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nasal congestion last 6 months	Reported odour of liquid sewage treatment	None or faint	1,08	0,89	1,32
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nasal congestion last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/very strong	1,09	0,86	1,38
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nasal congestion last 6 months	Reported odour of solid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nasal congestion last 6 months	Reported odour of solid sewage treatment	None or faint	0,94	0,71	1,24
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nasal congestion last 6 months	Reported odour of solid sewage treatment	Moderate/strong/very strong	1,05	0,79	1,39
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nasal congestion last 6 months	Reported livestock odour	None or faint	1		

Appendix S29. Non-allergic rhinitis, runny nose, blocked nose, itchy nose, Continued

NON-ALLERGIC RHINITIS, RUNNY, BLOCKED, ITCHY NOSE: 8 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nasal congestion last 6 months	Reported livestock odour	Moderate/strong/very strong	0,93	0,78	1,1
Wing 2014	Sewage treatment and AFO	Subj	Subj	Runny nose last 6 months	Reported odour of liquid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Runny nose last 6 months	Reported odour of liquid sewage treatment	None or faint	1,03	0,86	1,25
Wing 2014	Sewage treatment and AFO	Subj	Subj	Runny nose last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/very strong	0,79	0,58	1,07
Wing 2014	Sewage treatment and AFO	Subj	Subj	Runny nose last 6 months	Reported odour of solid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Runny nose last 6 months	Reported odour of solid sewage treatment	None or faint	0,99	0,78	1,25
Wing 2014	Sewage treatment and AFO	Subj	Subj	Runny nose last 6 months	Reported odour of solid sewage treatment	Moderate/strong/very strong	0,82	0,61	1,09
Wing 2014	Sewage treatment and AFO	Subj	Subj	Runny nose last 6 months	Reported livestock odour	None or faint	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Runny nose last 6 months	Reported livestock odour	Moderate/strong/very strong	1,16	0,98	1,38
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sneeze last 6 months	Reported odour of liquid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sneeze last 6 months	Reported odour of liquid sewage treatment	None or faint	1,09	0,87	1,37
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sneeze last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/very strong	1,01	0,73	1,38
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sneeze last 6 months	Reported odour of solid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sneeze last 6 months	Reported odour of solid sewage treatment	None or faint	1,2	0,89	1,6
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sneeze last 6 months	Reported odour of solid sewage treatment	Moderate/strong/very strong	1,05	0,75	1,47
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sneeze last 6 months	Reported livestock odour	None or faint	1		

Appendix S29. Non-allergic rhinitis, runny nose, blocked nose, itchy nose, Continued

NON-ALLERGIC RHINITIS, RUNNY, BLOCKED, ITCHY NOSE: 8 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sneeze last 6 months	Reported livestock odour	Moderate/strong/very strong	0,97	0,79	1,18
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Nasal congestion past 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Nasal congestion past 12 months	Odour zones from previous odour survey	High exposed	1,62	0,79	3,32

** Unadjusted models*

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Main results
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	Runny nose	Odour annoyance/distance (3 areas)/olfactometry	No difference between areas in the expected direction
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Runny nose	Distance (3 areas)	No difference between areas I, II and III

Appendix S30. Immune function/allergy

IMMUNE FUNCTION/ALLERGY: 4 studies

GENERAL POPULATION:
ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Avery 2004	AFO	Obj	Subj	IgA secretion rate (µg/min)	1-unit odour in previous 12 hours from 4 to 9 (odour scored from 0 to 9)	-0,05	-0,12	0,01
Avery 2004	AFO	Obj	Subj	IgA concentration (µg/ml)	1-unit odour in previous 12 hours from 4 to 9 (odour scored from 0 to 9)	-0,06	-0,12	0,01

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Prevalence of allergic symptoms in the last 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Prevalence of allergic symptoms in the last 12 months	Odour zones from previous odour survey	High exposed	1,04	0,51	2,11
Radon et al. 2007	AFO	Obj	Subj	IgE to common Allergens >0.35 IU/mL	Odour annoyance	Not at all	1		
Radon et al. 2007	AFO	Obj	Subj	IgE to common Allergens >0.35 IU/mL	Odour annoyance	Somewhat	1,11	0,79	1,57
Radon et al. 2007	AFO	Obj	Subj	IgE to common Allergens >0.35 IU/mL	Odour annoyance	Moderately	1,71	1,02	2,87
Radon et al. 2007	AFO	Obj	Subj	IgE to common Allergens >0.35 IU/mL	Odour annoyance	Strongly	1,02	0,51	2,03

** Unadjusted models*

WORKERS

Effect reported as mean difference between groups

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Tjalvin, G., et al. 2015	Chemical accident	Subj	Obj	Allergy score °	Workers living 20–30 km from the explosion site and who were neither employees in the industrial area nor clean-up workers	Controls	0		
Tjalvin, G., et al. 2015	Chemical accident	Subj	Obj	Allergy score°	Workers at the time of the explosion and/or clean-up workers	Exposed	0,5	-0.007	1

°Allergy score: asthma, breathing difficulties, eczema, allergies, chest pain experienced past month

Appendix S31. Eye irritation and itching eye

EYE IRRITATION, ITCHING EYE: 10 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Subj	Subj	Eye irritation after 10 minutes outdoor	Any odour in previous 12 hours (9-point scale)	0,53	0,41	0,65
Schinasi 2011	AFO	Subj	Subj	Itching eyes	Any odour in previous 12 hours (9-point scale)	0,17	-0,03	0,37
Schinasi 2011	AFO	Subj	Subj	Burning eyes previous 12 hours	Any odour in previous 12 hours (9-point scale)	0,32	0,12	0,52

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Segala 2003	Wastewater treatment	Subj	Obj	Eye irritation past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Eye irritation past 12 months	Distance (km)	1.5-3	1,12	0,91	1,39
Segala 2003	Wastewater treatment	Subj	Obj	Eye irritation past 12 months	Distance (km)	<1.5	1,05	0,84	1,31
Segala 2003	Wastewater treatment	Subj	Subj	Eye irritation past 12 months	Odour tolerance	Tolerant	1		
Segala 2003	Wastewater treatment	Subj	Subj	Eye irritation past 12 months	Odour tolerance	Moderately tolerant	2,19	1,81	2,65
Segala 2003	Wastewater treatment	Subj	Subj	Eye irritation past 12 months	Odour tolerance	Intolerant	3,22	2,42	4,29
Segala 2003	Wastewater treatment	Subj	Subj	Eye irritation past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Eye irritation past 12 months	Odour perception	Complaints with no impact in health	1,31	1,05	1,64
Segala 2003	Wastewater treatment	Subj	Subj	Eye irritation past 12 months	Odour perception	Complaints with impacts on health	2,29	1,66	3,15
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Eye irritation past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Eye irritation past 12 months	Distance (km)	1.5-3	1,2	0,8	1,8
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Eye irritation past 12 months	Distance (km)	<1.5	1,2	0,9	1,6

Appendix S31. Eye irritation and itching eye, Continued

EYE IRRITATION, ITCHING EYE: 10 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Eye irritation past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Eye irritation past 12 months	Odour perception	Yes	1,1	0,8	1,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Eye irritation past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Eye irritation past 12 months	Odour annoyance	Yes	1,5	1,1	2,1
Heaney 2011	Landfill	Subj	Subj	Eye irritation previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Eye irritation previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	5,3	2,5	11,6
Wing 2014	Sewage treatment and AFO	Subj	Subj	Eye irritation last 6 months	Reported odour of liquid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Eye irritation last 6 months	Reported odour of liquid sewage treatment	None or faint	0,83	0,61	1,14
Wing 2014	Sewage treatment and AFO	Subj	Subj	Eye irritation last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/very strong	0,95	0,63	1,43
Wing 2014	Sewage treatment and AFO	Subj	Subj	Eye irritation last 6 months	Reported odour of solid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Eye irritation last 6 months	Reported odour of solid sewage treatment	None or faint	0,95	0,64	1,42
Wing 2014	Sewage treatment and AFO	Subj	Subj	Eye irritation last 6 months	Reported odour of solid sewage treatment	Moderate/strong/very strong	1,12	0,72	1,76
Wing 2014	Sewage treatment and AFO	Subj	Subj	Eye irritation last 6 months	Reported livestock odour	None or faint	1		

Appendix S31. Eye irritation and itching eye, Continued

EYE IRRITATION, ITCHING EYE: 10 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Wing 2014	Sewage treatment and AFO	Subj	Subj	Eye irritation last 6 months	Reported livestock odour	Moderate/strong/very strong	0,99	0,75	1,29
Shustermann 1991	Multiple sites (petrochemical, landfill, sewage treatment, rubber industry)	Subj	Subj	Eye irritation	Odour perception	No	1		
Shustermann 1991	Multiple sites (petrochemical, landfill, sewage treatment, rubber industry)	Subj	Subj	Eye irritation	Odour perception	Yes	4,6	3,2	6,5
Lipscomb 1991	Hazardous waste site	Subj	Obj	Eye irritation past 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991	Hazardous waste site	Subj	Obj	Eye irritation past 12 months	Odour zones from previous odour survey	High exposed	1,89	0,93	3,88

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Main results
Kret, J., et al. 2018	Landfill	Subj	Obj	Eye irritation past 12 months	Distance (km)	No difference between landfill households and control households
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	Eye irritation	Odour annoyance/distance (3 areas)/olfactometry	No difference between areas in the expected direction
Deane and Sanders 1978*	Petrochemical plants	Subj	Obj	Eye irritation	Distance (3 areas)	No differences between areas

Appendix S32. Sore throat, dry throat, burning throat

SORE THROAT/DRY THROAT/IRRITATION/BURNING THROAT: 8 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Subj	Subj	Throat irritation after 10 minutes outdoor	Any odour in previous 12 hours (9-point scale)	0,41	0,29	0,53
Schinasi 2011	AFO	Subj	Subj	Sore throat previous 12 hours	Any odour in previous 12 hours (9-point scale)	0,08	-0,14	0,30

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Segala 2003	Wastewater treatment	Subj	Obj	Dry throat past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Dry throat past 12 months	Distance (km)	1.5-3	0,97	0,78	1,21
Segala 2003	Wastewater treatment	Subj	Obj	Dry throat past 12 months	Distance (km)	<1.5	0,95	0,74	1,2
Segala 2003	Wastewater treatment	Subj	Subj	Dry throat past 12 months	Odor tolerance	Tolerant	1		
Segala 2003	Wastewater treatment	Subj	Subj	Dry throat past 12 months	Odour tolerance	Moderately tolerant	2,04	1,68	2,48
Segala 2003	Wastewater treatment	Subj	Subj	Dry throat past 12 months	Odour tolerance	Intolerant	2,54	1,88	3,42
Segala 2003	Wastewater treatment	Subj	Subj	Dry throat past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Dry throat past 12 months	Odour perception	Complaints with no impact in health	0,97	0,75	1,25
Segala 2003	Wastewater treatment	Subj	Subj	Dry throat past 12 months	Odour perception	Complaints with impacts on health	1,92	1,36	2,71
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	dry throat past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	dry throat past 12 months	Distance (km)	1.5-3	0,9	0,6	1,3
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	dry throat past 12 months	Distance (km)	<1.5	1,3	1	1,8
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	dry throat past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	dry throat past 12 months	Odour perception	Yes	1,3	1	1,7

Appendix S32. Sore throat, dry throat, burning throat, Continued

SORE THROAT/DRY THROAT/IRRITATION/BURNING THROAT: 8 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	dry throat past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	dry throat past 12 months	Odour annoyance	Yes	1,5	1,1	2
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	sore throat past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	sore throat past 12 months	Distance (km)	1.5-3	1	0,7	1,5
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	sore throat past 12 months	Distance (km)	<1.5	0,9	0,6	1,2
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	sore throat past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	sore throat past 12 months	Odour perception	Yes	1	0,8	1,3
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	sore throat past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	sore throat past 12 months	Odour annoyance	Yes	1,3	0,9	1,8
Heaney 2011	Landfill	Subj	Subj	Burning throat previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Burning throat previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	3,3	1,5	7,1
Heaney 2011	Landfill	Subj	Subj	Sore throat previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Sore throat previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	1,9	0,8	4,2
Shustermann 1991	Multiple sites (petrochemical, landfill,	Subj	Subj	Sore throat	Odour perception	No	1		

Appendix S32. Sore throat, dry throat, burning throat, Continued

SORE THROAT/DRY THROAT/IRRITATION/BURNING THROAT: 8 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
	sewage treatment, rubber industry)								
Shustermann 1991	Multiple sites (petrochemical, landfill, sewage treatment, rubber industry)	Subj	Subj	Sore throat	Odour perception	Yes	4,3	2,8	6,7
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sore throat last 6 months	Reported odour of liquid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sore throat last 6 months	Reported odour of liquid sewage treatment	None or faint	1,13	0,86	1,48
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sore throat last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/very strong	1,21	0,86	1,72
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sore throat last 6 months	Reported odour of solid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sore throat last 6 months	Reported odour of solid sewage treatment	None or faint	1,41	0,97	2,04
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sore throat last 6 months	Reported odour of solid sewage treatment	Moderate/strong/very strong	0,74	0,45	1,21
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sore throat last 6 months	Reported livestock odour	None or faint	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Sore throat last 6 months	Reported livestock odour	Moderate/strong/very strong	1,08	0,85	1,36
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Sore throat in last month	Odour annoyance	No	1		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Sore throat in last month	Odour annoyance	Yes	1,35	0,9	2,04

Appendix S32. Sore throat, dry throat, burning throat, Continued

SORE THROAT/DRY THROAT/IRRITATION/BURNING THROAT: 8 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Sore throat 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Sore throat 12 months	Odour zones from previous odour survey	High exposed	2,64	1,25	5,59

**Unadjusted models*

Appendix S33. Nose irritation and burning nose

NOSE IRRITATION/BURNING NOSE: 8 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Subj	Subj	Nasal irritation after 10 minutes outdoor	Any odour in previous 12 hours (9-point scale)	0,65	0,55	0,75
Schinasi 2011	AFO	Subj	Subj	Nasal irritation previous 12 hours	Any odour in previous 12 hours (9-point scale)	0,46	0,21	0,71

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Nose irritation past 12 months	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Nose irritation past 12 months	Distance (km)	1.5-3	1,2	0,8	1,8
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Nose irritation past 12 months	Distance (km)	<1.5	1,5	1,1	2,1
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Nose irritation past 12 months	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Nose irritation past 12 months	Odour perception	Yes	1,2	0,9	1,6
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Nose irritation past 12 months	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Nose irritation past 12 months	Odour annoyance	Yes	1,3	0,9	1,9
Heaney 2011	Landfill	Subj	Subj	Burning nose previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Burning nose previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	5	2,5	10,2
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nose irritation last 6 months	Reported odour of liquid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nose irritation last 6 months	Reported odour of liquid sewage treatment	None or faint	0,77	0,48	1,26
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nose irritation last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/very strong	1,38	0,84	2,26
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nose irritation last 6 months	Reported odour of solid sewage treatment	Comparison area	1		

Appendix S33. Nose irritation and burning nose, Continued

NOSE IRRITATION/BURNING NOSE: 8 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nose irritation last 6 months	Reported odour of solid sewage treatment	None or faint	0,75	0,36	1,56
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nose irritation last 6 months	Reported odour of solid sewage treatment	Moderate/strong/very strong	1,17	0,66	2,1
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nose irritation last 6 months	Reported livestock odour	None or faint	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Nose irritation last 6 months	Reported livestock odour	Moderate/strong/very strong	0,76	0,51	1,13

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Main results
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	Nose irritation	Odour annoyance/distance (3 areas)/olfactometry	No difference between areas in the expected direction
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Nose irritation	Distance (3 areas)	No differences between areas

Appendix S34. General irritation symptoms

GENERAL IRRITATION SYMPTOMS: 2 studies

GENERAL POPULATION: ADULTS

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Effect size reported as a regression coefficient (β) for unit increase compared to reference									
Sucker 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Sum of irritant symptoms (Nose, Eye)	Log (odour frequency)		0,00	-0,11	0,18
Sucker 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Percent of residents with irritant symptoms (Nose, Eye)	Odour annoyance (11-point scale)		0,41	0,34	0,47
Effect size was reported as an odds ratio (OR)									
Sucker 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Percent of residents with irritant symptoms (Nose, Eye)	Odour annoyance intensity	Pleasant	1,00		
Sucker 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Percent of residents with irritant symptoms (Nose, Eye)	Odour annoyance intensity	Not-pleasant	1,10	0,70	1,60
Sucker 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Percent of residents with irritant symptoms (Nose, Eye)	Hedonic tone	Pleasant	1,00		
Sucker 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Percent of residents with irritant symptoms (Nose, Eye)	Hedonic tone	Not-pleasant	1,20	0,40	3,60
Heaney 2011	Landfill	Subj	Subj	Any mucous membrane irritation (burning eyes, nose, throat)	Any odour in previous 12-hr	No	1,00		
Heaney 2011	Landfill	Subj	Subj	Any mucous membrane irritation (burning eyes, nose, throat)	Any odour in previous 12-hr	Yes	3,70	2,00	7,10

Appendix S35. Skin disorders

SKIN DISORDERS: 6 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Schinasi 2011	AFO	Subj	Subj	Skin irritation after 10 minutes outdoor	Any odour in previous 12 hours (9-point scale)	0,37	0,06	0,68

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Itchy eczema lifetime	Distance (km)	3-5	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Itchy eczema lifetime	Distance (km)	1.5-3	1	0,6	1,5
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Obj	Itchy eczema lifetime	Distance (km)	<1.5	1,2	0,8	1,7
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Itchy eczema lifetime	Odour perception	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Itchy eczema lifetime	Odour perception	Yes	1,1	0,8	1,5
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Itchy eczema lifetime	Odour annoyance	No	1		
Aatamila, M., et al. 2011	Waste treatment + composting	Subj	Subj	Itchy eczema lifetime	Odour annoyance	Yes	1,1	0,8	1,5
Heaney 2011	Landfill	Subj	Subj	Itchy skin previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Itchy skin previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	1,9	0,6	5,6
Heaney 2011	Landfill	Subj	Subj	Skin irritation previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Skin irritation previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	4,7	1,1	21

Appendix S35. Skin disorders, Continued

SKIN DISORDERS: 6 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Heaney 2011	Landfill	Subj	Subj	Skin boils previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Skin boils previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	4,6	0,6	37,8
Heaney 2011	Landfill	Subj	Subj	Skin rash previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	No	1		
Heaney 2011	Landfill	Subj	Subj	Skin rash previous 12 hours	Any odour in previous 12 hours (5-point Likert scale)	Yes	1,2	0,2	6,3
Wing 2014	Sewage treatment and AFO	Subj	Subj	Skin rash last 6 months	Reported odour of liquid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Skin rash last 6 months	Reported odour of liquid sewage treatment	None or faint	1,66	0,91	3,03
Wing 2014	Sewage treatment and AFO	Subj	Subj	Skin rash last 6 months	Reported odour of liquid sewage treatment	Moderate/strong/very strong	2,21	1,13	4,32
Wing 2014	Sewage treatment and AFO	Subj	Subj	Skin rash last 6 months	Reported odour of solid sewage treatment	Comparison area	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Skin rash last 6 months	Reported odour of solid sewage treatment	None or faint	1,17	0,5	2,76
Wing 2014	Sewage treatment and AFO	Subj	Subj	Skin rash last 6 months	Reported odour of solid sewage treatment	Moderate/strong/very strong	1	0,41	2,46
Wing 2014	Sewage treatment and AFO	Subj	Subj	Skin rash last 6 months	Reported livestock odour	None or faint	1		
Wing 2014	Sewage treatment and AFO	Subj	Subj	Skin rash last 6 months	Reported livestock odour	Moderate/strong/very strong	0,75	0,44	1,28
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Skin irritation 12 months	Odour zones from previous odour survey	Comparison area	1		
Lipscomb 1991*	Hazardous waste site	Subj	Obj	Skin irritation 12 months	Odour zones from previous odour survey	High exposed	4,97	1,82	13,63

Appendix S35. Skin disorders, Continued

SKIN DISORDERS: 6 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Herr 2009	Composting site	Subj	Obj	Blotchiness or discolouration of the skin past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Blotchiness or discolouration of the skin past 2 years	Residents near composting site	EnvExp-2	1,15	0,5	2,61
Herr 2009	Composting site	Subj	Obj	Flushing or blushing past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Flushing or blushing past 2 years	Residents near composting site	EnvExp-2	1,2	0,61	2,38

** Unadjusted models*

Appendix S36. Mood states

MOOD STATES: 13 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Horton 2009	AFO	Subj	Subj	Nervous or anxious in previous 12 hours	Any odour in previous 12 hours (9-point scale)	0,47	0,34	0,59
Horton 2009	AFO	Subj	Subj	Angry, grouchy, bad-tempered in previous 12 hours	Any odour in previous 12 hours (9-point scale)	0,42	0,31	0,53
Horton 2009	AFO	Subj	Subj	Confused, poor concentration in previous 12 hours	Any odour in previous 12 hours (9-point scale)	0,27	0,15	0,41
Horton 2009	AFO	Subj	Subj	Gloomy, blue, unhappy in previous 12 hours	Any odour in previous 12 hours (9-point scale)	0,36	0,22	0,49
Steinheider 1998 (Nörvenich study)	AFO	Subj	Obj	Feeling miserable (7-point scale)	log (odour frequency from observation panel)	0,21	-0,08	0,49

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Radon 2004	AFO	Subj	Subj	Emotional SF-12 score	Odour annoyance	Not at all	1,00		
Radon 2004	AFO	Subj	Subj	Emotional SF-12 score	Odour annoyance	A little	0,33	0,44	0,67
Radon 2004	AFO	Subj	Subj	Emotional SF-12 score	Odour annoyance	Very much	0,10	0,03	0,33
Radon 2004	AFO	Subj	Subj	Emotional SF-12 score	Odour annoyance	Extremely	0,08	0,01	0,42
Heaney 2011	Landfill	Subj	Subj	Nervous or anxious	Any odour in previous 12 hours (5-point Likert scale)	No	1,00		
Heaney 2011	Landfill	Subj	Subj	Nervous or anxious	Any odour in previous 12 hours (5-point Likert scale)	Yes	2,50	1,30	5,00

Appendix S36. Mood states, Continued

MOOD STATES: 13 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Heaney 2011	Landfill	Subj	Subj	Angry, grouchy, bad-tempered	Any odour in previous 12 hours (5-point Likert scale)	No	1,00		
Heaney 2011	Landfill	Subj	Subj	Angry, grouchy, bad-tempered	Any odour in previous 12 hours (5-point Likert scale)	Yes	3,90	1,80	8,50
Heaney 2011	Landfill	Subj	Subj	Confused, poor concentration	Any odour in previous 12 hours (5-point Likert scale)	No	1,00		
Heaney 2011	Landfill	Subj	Subj	Confused, poor concentration	Any odour in previous 12 hours (5-point Likert scale)	Yes	0,30	0,03	2,10
Heaney 2011	Landfill	Subj	Subj	Stressed	Any odour in previous 12 hours (5-point Likert scale)	No	1,00		
Heaney 2011	Landfill	Subj	Subj	Stressed	Any odour in previous 12 hours (5-point Likert scale)	Yes	2,10	1,20	3,80
Heaney 2011	Landfill	Subj	Subj	Gloomy, blue, unhappy	Any odour in previous 12 hours (5-point Likert scale)	No	1,00		
Heaney 2011	Landfill	Subj	Subj	Gloomy, blue, unhappy	Any odour in previous 12 hours (5-point Likert scale)	Yes	3,10	1,60	6,10
Heaney 2011	Landfill	Subj	Subj	Active, energetic, peppy	Any odour in previous 12 hours (5-point Likert scale)	No	1,00		
Heaney 2011	Landfill	Subj	Subj	Active, energetic, peppy	Any odour in previous 12 hours (5-point Likert scale)	Yes	0,60	0,20	1,50
Herr 2009	Composting site	Subj	Obj	Sexual indifference past 2 years	Residents of neighbourhoods	Control	1,00		

Appendix S36. Mood states, Continued

MOOD STATES: 13 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Herr 2009	Composting site	Subj	Obj	Sexual indifference past 2 years	Residents near composting site	EnvExp-2	0,49	0,18	1,30
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Sadness (people with asthma) last month	Odour annoyance	No	1,00		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Sadness (people with asthma) last month	Odour annoyance	Yes	0,96	0,48	1,91
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Sadness (people with lower back pain) last month	Odour annoyance	No	1,00		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Sadness (people with lower back pain) last month	Odour annoyance	Yes	1,90	1,15	3,13
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Anxiousness last month	Odour annoyance	No	1,00		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Anxiousness last month	Odour annoyance	Yes	1,48	0,89	2,47
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Stress related symptoms (people with Asthma) last month	Odour annoyance	No	1,00		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Stress related symptoms (people with Asthma) last month	Odour annoyance	Yes	0,93	0,73	1,18
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Stress related symptoms (people with lower back pain) last month	Odour annoyance	No	1,00		
Hooiveld, M., et al. 2015	AFO	Subj	Subj	Stress related symptoms (people with lower back pain) last month	Odour annoyance	Yes	1,27	1,07	1,52
Lipscomb 1991*	Landfill	Subj	Obj	Nervous or anxious	Odour zones from previous odour survey	Comparison area	1,00		
Lipscomb 1991*	Landfill	Subj	Obj	Nervous or anxious	Odour zones from previous odour survey	High exposed	2,10	1,02	4,30

Appendix S36. Mood states, Continued

MOOD STATES: 13 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Lipscomb 1991*	Landfill	Subj	Obj	Confused, poor concentration	Odour zones from previous odour survey	Comparison area	1,00		
Lipscomb 1991*	Landfill	Subj	Obj	Confused, poor concentration	Odour zones from previous odour survey	High exposed	2,78	1,17	6,70
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Difficulty concentrating	Odour annoyance	Not annoyed	1,00		
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Difficulty concentrating	Odour annoyance	Slightly annoyed	1,95	0,83	4,61
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Difficulty concentrating	Odour annoyance	Moderately annoyed	5,06	1,63	15,70
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Subj	Difficulty concentrating	Odour annoyance	Very or extremely annoyed	9,03	2,90	28,20
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Difficulty concentrating	NH3 exposure, µg/m3	<2	1,00		
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Difficulty concentrating	NH3 exposure, µg/m3	2–3	1,38	0,60	3,19
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Difficulty concentrating	NH3 exposure, µg/m3	>3	2,05	0,86	4,86

** Unadjusted models*

Appendix S36. Mood states, Continued

MOOD STATES: 13 studies

GENERAL POPULATION: ADULTS

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Main results
Georgieff 1999	Paper plant	Subj	Obj	Decreased working capacity	Odour perception		Olfactory irritation decreased the working capacity
Georgieff 1999	Paper plant	Subj	Obj	Angry	Odour perception		No variation in symptom prevalence by olfactory irritation
Georgieff 1999	Paper plant	Subj	Obj	Nervous	Odour perception		No variation in symptom prevalence by olfactory irritation
Georgieff 1999	Paper plant	Subj	Obj	Depressed	Odour perception		No variation in symptom prevalence by olfactory irritation
Steinheider 1998 (Nettetal study)	AFO	Subj	Subj	Feeling miserable	Distance from the odour source (adjustment for odour annoyance)		Higher symptom-reporting with increasing distance from the odour source
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Nervousness reported frequently or occasionally	Distance (3 areas)		No difference between areas I, II and III
Deane and Sanders 1977	Paper plant	Subj	Subj	Nervousness	Odour annoyance/ distance (3 areas)		No difference between areas I, II and III or odour annoyance
Hayes 2017	Wastewater treatment plant	Subj	Subj	Perceived control (Likert 4 categories)	Odour impacting on health	No/Yes	Association with odour complaint near to significant after adding social readjustment scale as covariate
Hayes 2017	Wastewater treatment plant	Subj	Subj	Depression (Likert 4 categories)	Odour impacting on health	No/Yes	Association with odour complaint near to significant after adding social readjustment scale as covariate

WORKERS

Effect reported as mean difference between groups

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Tjalvin, G., et al. 2017	Chemical accident	Subj	Subj	Total IES-R* score	Odour score	Low odour score	0		
Tjalvin, G., et al. 2017	Chemical accident	Subj	Subj	Total IES-R* score	Odour score	High odour score	3,7	2,03	5,37

** IES-R (Impact of Event Scale-Revised)*

Appendix S37. Cardiovascular problems

CARDIOVASCULAR PROBLEMS: 3 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Wing 2013	AFO	Obj	Subj	SBP (systolic)	Any odour in previous 12 hours (9-point scale	0,10	0,07	0,39
Wing 2013	AFO	Obj	Subj	DBP (diastolic)	Any odour in previous 12 hours (9-point scale)	0,23	-0,01	0,34

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Herr 2009	Composting site	Subj	Obj	Palpitation past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Palpitation past 2 years	Residents near composting site	EnvExp-2	0,99	0,55	1,77
Herr 2009	Composting site	Subj	Obj	Discomfort around the precordium past 2 years	Residents of neighbourhoods	Control	1		
Herr 2009	Composting site	Subj	Obj	Discomfort around the precordium past 2 years	Residents near composting site	EnvExp-2	1,55	0,77	3,11
Segala 2003	Wastewater treatment	Subj	Obj	Hypertension past 12 months	Distance (km)	3-5	1		
Segala 2003	Wastewater treatment	Subj	Obj	Hypertension past 12 months	Distance (km)	1.5-3	0,83	0,68	1,01
Segala 2003	Wastewater treatment	Subj	Obj	Hypertension past 12 months	Distance (km)	<1.5	0,82	0,67	1,01
Segala 2003	Wastewater treatment	Subj	Subj	Hypertension past 12 months	Odour tolerance	Tolerant	1		
Segala 2003	Wastewater treatment	Subj	Subj	Hypertension past 12 months	Odour tolerance	Moderately tolerant	1,15	0,92	1,46
Segala 2003	Wastewater treatment	Subj	Subj	Hypertension past 12 months	Odour tolerance	Intolerant	1,31	0,91	1,89
Segala 2003	Wastewater treatment	Subj	Subj	Hypertension past 12 months	Odour perception	No complaints	1		
Segala 2003	Wastewater treatment	Subj	Subj	Hypertension past 12 months	Odour perception	Complaints with no impact in health	1,24	0,93	1,65
Segala 2003	Wastewater treatment	Subj	Subj	Hypertension past 12 months	Odour perception	Complaints with impacts on health	1,39	0,91	2,14

Appendix S38. Odour nuisances

ODOUR NUISANCES: 10 studies

GENERAL POPULATION: ADULTS

Effect size reported as a regression coefficient (β) for unit increase compared to reference

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Value	95% CI inf	95% CI sup
Steinheider et al. 1998 (Nörvenich study)	AFO	Subj	Obj	Odour annoyance	log (odour frequency from observation panel)	2,90	2,19	3,61
Sucker et al. 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Odour annoyance	log (odour frequency)	0,47	0,26	0,69
Sucker et al. 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Serious odour annoyance	log (odour frequency)	0,64	0,26	0,96

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Odour annoyance (annoyed vs. not annoyed)	NH3 exposure, µg/m3	<2	1		
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Odour annoyance (annoyed vs. not annoyed)	NH3 exposure, µg/m3	2–3	2,5	1,55	4,05
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Odour annoyance (annoyed vs. not annoyed)	NH3 exposure, µg/m3	>3	4,17	2,4	7,23

Appendix S38. Odour nuisances, Continued

ODOUR NUISANCES: 10 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Odour annoyance (moderately, very or extremely annoyed vs. not or slightly annoyed)	NH3 exposure, µg/m3	<2	1		
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Odour annoyance (moderately, very or extremely annoyed vs. not or slightly annoyed)	NH3 exposure, µg/m3	2–3	5,97	2,6	13,7
Blanes-Vidal, V. 2015	Storage and treatment of farming and agricultural waste	Subj	Obj	Odour annoyance (moderately, very or extremely annoyed vs. not or slightly annoyed)	NH3 exposure, µg/m3	>3	9,28	3,86	22,3
Sucker et al. 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Odour annoyance	Odour intensity	Pleasant	1		
Sucker et al. 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Odour annoyance	Odour intensity	Not-pleasant	1,3	1,1	1,5
Sucker et al. 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Odour annoyance	Hedonic tone	Pleasant	1		
Sucker et al. 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Odour annoyance	Hedonic tone	Not-pleasant	4,9	3,4	7,2
Sucker et al. 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Serious odour annoyance	Odour intensity	Pleasant	1		
Sucker et al. 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Serious odour annoyance	Odour intensity	Not-pleasant	1,5	1,1	2

Appendix S38. Odour nuisances, Continued

ODOUR NUISANCES: 10 studies

GENERAL POPULATION: ADULTS

Effect size was reported as an odds ratio (OR)

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Subcategory	Value	95% CI inf	95% CI sup
Sucker et al. 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Serious odour annoyance	Hedonic tone	Pleasant	1		
Sucker et al. 2008	Multiple industries (bakery, oil, metallurgic, sweets, textile, fat refinery)	Subj	Subj	Serious odour annoyance	Hedonic tone	Not-pleasant	17,5	6,7	46,5
Horton et al. 2009	AFO	Subj	Subj	Odour annoyance	12-h mean odour 9-point scale	No	1		
Horton et al. 2009	AFO	Subj	Subj	Odour annoyance	12-h mean odour 9-point scale	Yes	1,81	1,63	2
Boers et al. 2016	AFO	Subj	Obj	Odour annoyance from livestock farming in general	lnP98 hourly odour exposure	No	1		
Boers et al. 2016	AFO	Subj	Obj	Odour annoyance from livestock farming in general	lnP98 hourly odour exposure	Yes	1,88	1,48	2,38
Boers et al. 2016	AFO	Subj	Obj	Odour annoyance from livestock housings	lnP98 hourly odour exposure	No	1		
Boers et al. 2016	AFO	Subj	Obj	Odour annoyance from livestock housings	lnP98 hourly odour exposure	Yes	2,04	1,39	3,01
Boers et al. 2016	AFO	Subj	Obj	Odour annoyance from spreading slurry and manure	lnP98 hourly odour exposure	No	1		
Boers et al. 2016	AFO	Subj	Obj	Odour annoyance from spreading slurry and manure	lnP98 hourly odour exposure	Yes	1,63	1,28	2,08

Appendix S38. Odour nuisances, Continued

ODOUR NUISANCES: 10 studies

GENERAL POPULATION: ADULTS

No association estimate in the study

Study	Source	Type of outcome	Type of exposure	Outcome variable	Exposure variable	Main results
Deane and Sanders 1978	Petrochemical plants	Subj	Obj	Odour annoyance	Distance (3 areas)	Significant reduction in prevalence of annoyance by areas (from Area I "most exposed" to Area III "less exposed")
Deane and Sanders 1978	Petrochemical plants	Subj	Subj	Actions taken concerning odour problem	Distance (3 areas)/odour annoyance	Among very much bothered by odour, residents in Area I and II were more apt to request action or to consider moving out than residents from Area III
Deane and Sanders 1977	Paper plant	Subj	Subj/Obj	Odour annoyance	Distance (3 areas)	No clear association between distance and annoyance
Kret, J., et al. 2018	Landfill	Subj	Obj	Noticed a bad smell in the last 12 months	Distance (Exposed area vs not exposed area)	Landfill residents had a higher probability of reporting of annoyance
Kret, J., et al. 2018	Landfill	Subj	Obj	Worried about environmental issues in the neighbourhood	Distance (Exposed area vs not exposed area)	Landfill residents had a higher probability of reporting of environmental worry
Shustermann 1991	Multiple sites (petrochemical, landfill, sewage treatment, rubber industry)	Subj	Subj	Environmental worry	Odour perception	Frequency of odour perception tends to increase with increasing level of environmental worry
Lipscomb 1991*	Landfill	Subj	Obj	Odour detection	Odour zones from previous odour survey	Higher odor detection in exposed areas

* *Unadjusted models*