UMWELT & GESUNDHEIT
06/2023

Quantifizierung der Krankheitslast verursacht durch Ozon-Exposition in Deutschland für die Jahre 2007-2016

Abschlussbericht - Teil 2: Anhang

Für Mensch & Umwelt

Umwelt Bundesamt

UMWELT & GESUNDHEIT 06/2023

Ressortforschungsplan des Bundesministerium für
Umwelt, Naturschutz und nukleare Sicherheit

Forschungskennzahl 3718 62 208 0
FB000489/2

Quantifizierung der Krankheitslast verursacht durch Ozon-Exposition in Deutschland für die Jahre 2007-2016

Abschlussbericht - Teil 2: Anhang

von

Susanne Breitner, Nadine Steckling-Muschack, Iana
Markevych, Tianyu Zhao, Hanna Mertes, Joachim
Heinrich, Dennis Nowak

Klinikum der Universität München, Institut und Poliklinik für
Arbeits-, Sozial- und Umweltmedizin, Unit Global
Environmental Health, München

Im Auftrag des Umweltbundesamtes

Impressum

Herausgeber
Umweltbundesamt
Wörlitzer Platz 1
06844 Dessau-Roßlau
Tel: +49 340-2103-0
Fax: +49 340-2103-2285
buergerservice@uba.de
Internet: www.umweltbundesamt.de

/umweltbundesamt.de
/umweltbundesamt

Durchführung der Studie:
Klinikum der Universität München, Ludwig-Maximilians-Universität München, Institut und Poliklinik für Arbeits-, Sozial- und Umweltmedizin, Unit Global Environmental Health
Ziemssenstr. 1
80366 München

Abschlussdatum:
November 2020

Redaktion:
Fachgebiet II 1.6 Expositionsschätzung, gesundheitsbezogene
Indikatoren Dirk Wintermeyer

Publikationen als pdf:
http://www.umweltbundesamt.de/publikationen

ISSN 1868-4340

Dessau-Roßlau, August 2023

Das diesem Bericht zu Grunde liegende Vorhaben wurde aus Mitteln des Bundesministeriums für Umwelt, Naturschutz und nukleare Sicherheit im Rahmen des Ressort-Forschungsplans 2018 finanziert.

Kurzbeschreibung: Quantifizierung der Krankheitslast verursacht durch Ozon-Exposition in Deutschland für die Jahre 2007-2016

Dieses Vorhaben erfasst die flächendeckende Hintergrund-Ozonexposition der Bevölkerung Deutschlands während der Sommermonate (mittlere maximale 8-Stundenkonzentration in den Monaten April bis September) sowie durch den SOMO35 (als jährliche Summe über die täglichen Maxima der 8-stündigen gleitenden Mittelwerte, die 35 ppb (parts per billion) überschreiten) mit anschließender Quantifizierung der Krankheitslast für die Jahre 2007 bis 2016 durchgeführt.

Umfangreiche systematische Literatur-Recherchen nach der Methodik des Umbrella Reviews und des Systematic Mappings, in das neben epidemiologischen Studien auch Ergebnisse experimenteller Studien eingeflossen sind, fassen die Evidenz zur kausalen Wirkung langfristiger Expositionen gegenüber Ozon auf die respiratorische und die COPD-Mortalität zusammen. Die identifizierten Risikoschätzer aus epidemiologischen Kohortenstudien mit langfristiger Expositionsschätzung für Ozon und den genannten Gesundheitsendpunkten wurden nach einer Metaanalyse im Hinblick auf die Krankheitslastschätzung verwendet.

Der attributable Anteil (also der Anteil der Krankheitslast, der mittels statistischer Verfahren auf Sommer-Ozon zurückgeführt werden kann) an der respiratorischen Krankheitslast aufgrund von Sommer-Ozon lag im Bereich von 4,03 % (95% Konfidenzintervall (KI): 2,55-5,64) (Jahr 2013) bis 5,49 % (95% KI: 3,48-7,66) (Jahr 2015); der Schätzer für verlorene Lebensjahre (YLL, Years of Life Lost) pro 100.000 Einwohnenden lag im Bereich von 26,53 YLL (95% KI: 16,76-37,12) (Jahr 2007) bis 43,44 YLL (95% KI: 27,53-60,59) (Jahr 2015). Für die COPD-Krankheitslast variierte der attributable Anteil und der Schätzer für YLL aufgrund von Sommer-Ozon im Bereich von 6,11 % (95% KI: 4,68-7,36) (Jahr 2013) bis 8,29 % (95% KI: 6,36-9,96) (Jahr 2015) bzw. 18,33 YLL pro 100.000 Einwohnenden (95% KI: 14,02-22,08) (Jahr 2007) bis 35,77 YLL pro 100.000 Einwohnenden (95% KI: 27,45-42,98) (Jahr 2015). Insgesamt ist im Zeitraum 2007 bis 2016 kein eindeutiger zeitlicher Trend in der Krankheitslast zu erkennen – im Beobachtungszeitraum von 10 Jahren war eine Schwankung der relativen Krankheitslast von mehr als einem Drittel von Jahr zu Jahr zu beobachten, ähnlich den Unterschieden der Ozon-Konzentrationen. Ein Vergleich der Ergebnisse der Krankheitslastschätzung durch Ozon mit jenen nach einer zusätzlichen Adjustierung der Effektschätzer für Feinstaub ($PM_{2.5}$) und Stickstoffdioxid (NO_2) zeigt eine etwas niedrigere respiratorische Krankheitslast, aber eine höhere COPD-Krankheitslast. Dabei ist jedoch zu berücksichtigen, dass die quantitative Zusammensetzung der Außenluftschadstoffe in Nordamerika (fast alle berücksichtigten Studien wurden dort durchgeführt) sich von derjenigen in Deutschland unterscheidet. Hinzu kommen Unterschiede bei der Berechnung der Krankheitslast dadurch zu Stande, dass sich die verwendeten Risikoschätzer deutlich unterscheiden. Die Krankheitslastschätzungen durch Ozon zwischen den verschiedenen Studien sind wegen der unterschiedlich verwendeten Eingangsdaten mit Vorsicht zu vergleichen. Zudem sind Vergleiche der Krankheitslastschätzungen durch Ozon mit den feinstaubbedingten oder NO_2-bedingten Studien wegen unterschiedlicher Eingangsdaten nur mit Vorsicht anzustellen. Qualitative Vergleiche weisen allerdings auf eine niedrigere Krankheitslast durch Langzeitexposition mit Ozon im Vergleich zu Feinstaub und NO_2 hin. Trotz der inhärenten Unsicherheiten und Limitierungen halten wir die Ergebnisse dieses Vorhabens, die der langfristigen Exposition mit Ozon einen kausalen Beitrag an der respiratorischen Krankheitslast, unabhängig von Feinstaub und NO_2 zuschreiben, insgesamt für belastbar.

Abstract: Quantification of the burden of disease caused by ozone exposure in Germany for the years 2007-2016

This project describes a nationwide estimation of the background ozone exposure of the German population during the summer months (as an average of the daily 8-hour maximum ozone concentration from April to September) and SOMO35 (as an annual sum over the daily maxima of the 8-hour moving averages exceeding 35 ppb (parts per billion)) was carried out, followed by quantification of the disease burden for the years 2007 to 2016.

Extensive systematic literature reviews using the methodology of the Umbrella Review and Systematic Mapping, which included epidemiological studies as well as results of experimental studies, summarise the evidence on the causal effect of long-term exposure to ozone on respiratory and COPD mortality. The identified risk estimates from epidemiological cohort studies on long-term exposure to ozone and the health outcomes mentioned above were pooled in a meta-analysis; the combined estimates were used for the disease burden estimation.

The attributable fraction of the respiratory disease burden and the years of life lost (YLL) estimates per 100,000 inhabitants due to summer ozone ranged from 4.03 % (Confidence Interval (CI): 2.55-5.64) (year 2013) to 5.49 % (95% CI: 3.48-7.66) (year 2015) and from 26.53 YLL (95% CI: 16.76-37.12) (year 2007) to 43.44 YLL (95% CI: 27.53-60.59) (year 2015) respectively. For the COPD disease burden, the attributable fraction and the estimate for YLL due to summer ozone varied from 6.11 % (95% CI: 4.68-7.36) (year 2013) to 8.29 % (95% CI: 6.36-9.96) (year 2015) and 18.33 YLL per 100,000 inhabitants (95% CI: 14.02-22.08) (year 2007) to 35.77 YLL per 100,000 inhabitants (95% CI: 27.45-42.98) (year 2015). Overall, no clear temporal trend of the attributable burden can be discerned in the period 2007 to 2016. In the 10-year observation period, a fluctuation in the relative attributable burden of more than a third from year to year was observed, similar to the differences in ozone concentrations. A comparison of the results of the disease burden due to summer ozone with those after additional adjustment for fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) shows a slightly lower disease burden for respiratory mortality but a higher one for COPD mortality. However, it should be noted that the quantitative composition of outdoor air pollutants in North America (almost all studies considered were conducted there) differs from that in Germany. In addition, there are differences in the calculation of the disease burden since the risk estimates used differ significantly. A reliable quantitative comparison of the estimates of the burden of disease caused by ozone between the different studies is challenging, because of the different input data used. In addition, comparisons of the disease burden estimates for ozone with those for PM or NO_2 are to be made with the greatest caution because of the different input data. Qualitative comparisons, however, indicate a lower burden of disease from long-term exposure to ozone compared to PM and presumably also to NO_2. Despite the inherent uncertainties and limitations, we consider the results of this project, which attribute a causal contribution to the respiratory disease burden to long-term exposure to ozone, independent of PM and NO_2, to be robust overall.

Inhaltsverzeichnis

Abbildungsverzeichnis

Tabellenverzeichnis

Abkürzungsverzeichnis

39. BImSchV	39. Verordnung zur Durchführung des Bundes-Immissionsschutzgesetzes
AP	Air pollution
ACS	American Cancer Society
AF	Atrial fibrillation
AHR	Atemwegshyperreagibilität
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
APHENA	APHENA: The Air Pollution and Health: A European and North American Approach
AP(s)	Arbeitspaket(e)
ASD(s)	Autism spectrum disorder(s)
AZ	Arizona
BALF	Bronchoalveolar lavage fluid
BHR	Bronchial hyperresponsiveness
BMU	Bundesministerium für Umwelt, Naturschutz und nukleare Sicherheit
BoD	Burden of Disease (Krankheitslast)
BP	Blood pressure
BStatG	Bundesstatistikgesetz
CA	California
CanCHEC	Canadian Census Health and Environment Cohort
CI	Confidence interval (Konfidenzintervall)
CO	Kohlenmonoxid
CO	Colorado (Bundesstaat)
COPD	Chronisch obstruktive Lungenerkrankung
CPC	Comprehensive Pneumology Center
CPRD	Clinical Practice Research Datalink
CSC	China Scholarship Council
CSE	Cigarette smoke extract
CVD	Cardiovascular diseases (kardiovaskuläre Erkrankungen)
DALY(s)	Disability-adjusted Life Year(s)
DBP	Diastolic blood pressure
DMA	Dimethylacetoacetamide
DMSO	Dimethylsulfoxide
DNA	Desoxyribonukleinsäure
DW(s)	Disability weight(s)

DZL	Deutsches Zentrum für Lungenforschung
E	Osten
EBD	Environmental Burden of Disease (Umweltbedingte Krankheitslast)
EBoDE	Environmental Burden of Disease in European countries
ED	Emergency department visits (Einweisung in ein Krankenhaus oder Notaufnahme
EPPI	Evidence for Polica and Practice Information and Coordinating Centre
ER	Excess risk
ERV(s)	Emergency room visit(s)
EW	Einwohnende
EWF	Expositions-Wirkungs-Funktion
FA	Filtered Air
FEV	Forced expiratory volume
FKZ	Forschungskennzahl
FVC	Forced vital capacity
g	Gramm
GBD	Global Burden of Disease
GDM	Gestational diabetes mellitus
GEniUS	Gesundheitsökonomie und Environmental Burden of Disease im Umweltschutz
GIS	Geographische Informationssysteme
HDMA	Dermatophagoides farina
HDP	Hypertensive disorders of pregnancy
Hg	Quecksilber
HIC(s)	High income country (countries)
HR	Hazard ratio
hr(s)	Hours (Stunden)
ICD	International Classification of Diseases
IHME	Institute for Health Metrics and Evaluation
ISI	Institute for Scientific Information
JBI	Joanna Briggs Institute
KI	Konfidenzintervall
kg	Kilogramm
km	Kilometer
L	Liter
LBW	Low birth weight
LCA	Life cycle assessment (LCA) (Einschätzung im Lebenszyklus)

LfU	Bayerisches Landesamt für Umwelt
LMIC	Low- and middle-income countries
LMU	Ludwig-Maximilians-Universität München
LRS	Lower respiratory symptoms (Symptome der unteren Atemwege)
m^2	Quadratmeter
m^3	Kubikmeter
MA	Massachusetts
MD	Maryland
ME	Maine
MEDLARS	Medical literature analysis and retrieval system
MEDLINE	Medical literature analysis and retrieval system online
mg	Milligramm
min	Minute(n)
mL	Milliliter
mm	Millimeter
MRDAs	Minor restricted activity days
N	Norden
na	Not applicable
NaHS	Sodium hydrosulfide
NCBI	National Center for Biotechnology Information
NIH	National Institutes of Health (U.S.)
NLM	National Library of Medicine (U.S.)
NN	nomen nescio (noch zu nennender Name)
NO	Stickstoffmonoxid
NO_x	Stickstoffoxide
NO_2	Stickstoffdioxid
NTP	National Toxicological Program
NY	New York (Bundesstaat)
O_3	Ozon
OECD	Organisation for Economic Co-operation and Development (Organisation für wirtschaftliche Zusammenarbeit und Entwicklung)
OHAT	Office of Health Assessment and Translation
OHCA	Out-of-hospital cardiac arrest
OI	Optimale Interpolation
OR	Odds ratio
PAF	Population attributable fraction (PAF) (Attributabler Anteil)

PBS	Phosphate-buffered saline
PD	Parkinson’s Disease
PECO	Population, exposure, comparator, outcome
PICO	Population, intervention, comparator, outcome
PM	Particulate matter (Feinstaub)
PM_{10}	Particulate matter below 10 µg
$PM_{2.5}$	Particulate matter below 2.5 µg
ppb	Parts per billion
ppm	Parts per million
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRISMA-P	Preferred reporting items for systematic review and meta-analysis protocols
PROSPERO	International prospective register of systematic reviews
PTB	Preterm birth
ReFoPlan	Ressortforschungsplan
RCG	REM/CALGRID (Transportmodell)
RIVM	National Institute for Public Health and the Environment
RR	Relatives Risiko
S	Süden
SCIE	Social Care Institute for Excellence
SBP	Systolic blood pressure
SEM(s)	Systematic Map(s), Mapping Reviews oder auch Systematic Evidence Maps
SGA	Small for gestational age
SOMO35	Sum of ozone means over 35 ppb, Summe der Ozonmittelwerte über 35 ppb
SR	Systematic review
Tox. Review	Systematischer Literaturreview von experimentellen Studien zur Prüfung der biologischen Plausibilität von ausgewählten epidemiologisch bestätigten Gesundheitsendpunkten
UBA	Umweltbundesamt
UK	United Kingdom
UMIT	University for Health Sciences, Medical Computer Science and Technology
UNECE	United Nations Economic Commission for Europe
UR	Unit Risk
U.S. EPA	United States Environmental Protection Agency
UV	Ultraviolett
VegAS	Verteilungsbasierte Analyse gesundheitlicher Auswirkungen von Umwelt-Stressoren
VOC(s)	Volatile Organic Compound(s) (flüchtige organische Verbindung(en))

vs	Versus
VSD	Ventricular septal defect
W	Westen
wk(s)	Week(s)
WoE	Weight-of Evidence
WHO	World Health Organization (Weltgesundheitsorganisation)
WoS	Web of Science
YLD	Year Lived with Disability
YLL	Year of Life Lost due to premature death

Zusammenfassung

Hintergrund

Das Umweltbundesamt (UBA) hat das Projekt „Quantifizierung der Krankheitslast verursacht durch Ozon-Exposition in Deutschland für die Jahre 2007-2016“ initiiert. Hintergrund der Ausschreibung ist zum einen die zeitliche Veränderung der Ozonkonzentrationen in Deutschland, die sich durch eine leicht steigende mittlere Ozonkonzentration bei gleichzeitigem leichtem Rückgang der Spitzenkonzentrationen beschreiben lassen (1995-2017) (UBA 2019b). Durch den Klimawandel ist auch mit weiteren zeitlichen Veränderungen der Ozonkonzentrationen in Deutschland zu rechnen. Darüber hinaus sind die gesundheitlichen Wirkungen des bodennahen Ozons im Vergleich zu Feinstaub und NO_2 in der Forschung der letzten 20-30 Jahre vernachlässigt worden (Zhao et al. 2019), obwohl die Organisation for Economic Co-operation and Development (OECD) bodennahes Ozon neben Feinstaub als die wichtigsten gesundheitsrelevanten Risikofaktoren in der Außenluft erachtet (OECD 2012).

Bodennahes Ozon

Das Spurengas Ozon ist ein natürlich vorkommender Bestandteil der Luft und liegt unter normalen atmosphärischen Bedingungen gasförmig vor (Bayerisches Landesamt für Umwelt, LfU 2018). Als ein aus drei Sauerstoffatomen bestehendes Molekül (Summenformel O_3) ist Ozon sehr reaktiv und eines der stärksten Oxidationsmittel (Zhang et al. 2019). Ozon wird nicht direkt emittiert, sondern als sekundärer Luftbestandteil über komplexe photo-chemische Reaktionen bei Vorliegen von Vorläufersubstanzen und höheren Temperaturen gebildet (Lumb 2017, U.S. EPA 2013). Dabei ist – plakativ gesagt – zwischen „gutem“ stratosphärischem und „schlechtem“ troposphärischem Ozon zu unterscheiden (Zhang et al. 2019). Stratosphärisches Ozon macht ca. 90 % des vorkommenden Ozons aus und absorbiert als das Leben auf der Erde schützende Ozonschicht einen Großteil der schädlichen ultravioletten (UV) Strahlung. Troposphärisches, sogenanntes bodennahes, Ozon hingegen wirkt reizend und schädigend auf Zellen von Pflanzen, Tieren und Menschen. Bodennahes Ozon stammt zu einem geringen Teil aus den oberen Luftschichten, wird jedoch größtenteils, vor allem beginnend im Frühjahr mit Anstieg der Temperaturen und einer verstärkten Sonneneinstrahlung, mittels UV-Strahlung aus den Vorläufersubstanzen Stickstoffoxid (NO_x), Kohlenmonoxid (CO) und flüchtigen organischen Verbindungen (Volatile Organic Compound(s), VOCs) natürlichen und anthropogenen Ursprungs gebildet (Zhang et al. 2019, LfU 2018).

Der aktuelle Wissensstand zu bodennahem Ozon und insbesondere zu dessen gesundheitlichen Wirkungen wird durch die kürzlich veröffentlichte Darstellung des Expertenberichtes der amerikanischen Umweltbehörde U.S. EPA (2020) hervorragend zusammengefasst.

Gemäß den pathophysiologischen Reaktionen werden insbesondere respiratorische Gesundheitseffekte bei Menschen auf kurzzeitige Expositionen mit Ozon zurückgeführt. Die Evidenz zum Zusammenhang von Ozon und Krebs ist laut U.S.EPA (2013) vergleichsweise gering. Auch bezüglich kardiovaskulärer Gesundheitseffekte bestehen Unsicherheiten in der wissenschaftlichen Datenlage, da relativ wenig Kenntnis darüber besteht, wie Ozon auf das kardiovaskuläre System wirkt (Zhang et al. 2019). Zum Schutz der menschlichen Gesundheit definiert die 39. Verordnung zur Durchführung des Bundes-Immissionsschutzgesetzes (39. BImSchV) Zielwerte, die sich auf mittlere Konzentrationen (gleitende maximale 8-Stundenmittelwerte) beziehen. Zusätzlich ist festgelegt, dass die Bevölkerung bei hohen Ozonwerten zu informieren und zu warnen ist (Informations- und Alarmschwellen).

Projektziele

Das Hauptziel des Projektes besteht darin, die Krankheitslast, die durch Langzeitexpositionen mit Ozon verursacht wird, für die Bevölkerung in Deutschland zu quantifizieren. Dafür werden die folgenden Einzelziele verfolgt:

1. Flächendeckende Erfassung der bevölkerungsbezogenen Exposition gegenüber Ozon während der Sommermonate (April bis September) und die Summe von Ozonwerten über 35 ppb im Verlaufe eines Jahres (SOMO35) in Deutschland für die Jahre 2007-2016.
2. Identifizierung epidemiologischer Studien zur gesundheitlichen Wirkung von bodennahem Ozon (Umbrella Review) und speziell die Identifizierung von Gesundheitsendpunkten mit einer kausalen Wirkung nach Einbeziehung experimenteller Studien in die systematischen Reviews (Systematic Mapping).
3. Quantifizierung der Krankheitslast verursacht durch Ozon in Form von Years Lived with Disability (YLD), Years of Life Lost (YLL) und Disability-Adjusted Life Years (DALYs).
4. Schätzung der Krankheitslast durch Ozon nach Adjustierung für weitere Luftschadstoffe (Feinstaub, NO_2) und Temperatur.

Methoden

Das Projekt besteht aus den folgenden fünf Arbeitspaketen (AP). AP 1, 2 und 3 bilden die Grundlage für AP 4. AP 5 hat eine übergreifende Funktion und ist in allen anderen AP angesiedelt. Im Projektverlauf wurde AP 1 durch eine Projektaufstockung erweitert; AP 2 und 3 wurden zusammengelegt.

Arbeitspaket (AP) 1: Literaturrecherche

AP 1 umfasst eine systematische Literaturrecherche zum aktuellen wissenschaftlichen Erkenntnisstand zu den gesundheitlichen Wirkungen von Ozon (Morbidität und Mortalität). Anhand einer systematischen Literaturrecherche werden die gesundheitlichen Wirkungen sowie die zugehörigen Effektschätzer recherchiert, die den Zusammenhang zwischen Exposition und Wirkung beschreiben. Berücksichtigt werden Morbidität und Mortalität, Kurzzeit- und Langzeiteffekte sowie Kombinationswirkungen (Ozon im Zusammenhang mit weiteren Luftschadstoffen und der Temperatur), um ein möglichst umfassendes Bild zu den durch Ozon verursachten gesundheitlichen Wirkungen zu erhalten.

Projektaufstockung: Biologische Plausibilität

Im Rahmen des Projektes war ursprünglich geplant, lediglich die epidemiologische Evidenz der möglichen ozonassoziierten Gesundheitsendpunkte im Rahmen eines systematischen Reviews zu überprüfen. Das entspricht nicht mehr dem aktuellen Stand zu systematischen Reviews, bei dem explizit die Einbeziehung experimenteller Studien gefordert wird (National Toxicology Program [NTP] 2015). Zur Stärkung der im Ozon-Projekt zusammengetragenen Evidenz wurde das Projekt wie folgt erweitert: Erstellung eines zusätzlichen systematischen Literaturreviews einschließlich experimenteller Studien (tierexperimentelle und mechanistische/in vitro-Studien) zur Prüfung der biologischen Plausibilität von ausgewählten epidemiologisch bestätigten Gesundheitsendpunkten. Durch die Einbeziehung experimenteller Studien konnte die Kausalität des in epidemiologischen

Studien nachgewiesenen Zusammenhangs zwischen der Ozon-Exposition und den jeweiligen gesundheitlichen Effekten bestätigt werden.

AP 2 und AP 3: Expositionsschätzung

AP 2 und AP 3 beinhalten die Schätzung der flächendeckenden bevölkerungsbezogenen Ozon-Exposition in Deutschland für den Zeitraum 2007 bis 2016 speziell für die Sommermonate und den SOMO35 (jährliche Summe der täglichen Maxima der gleitenden 8-Stundenmittelwerte unter Berücksichtigung der Tage mit Ozonwerten über 35 ppb bzw. 70 µg/m^3). Der Bevölkerung Deutschlands wird räumlich hoch aufgelöst eine Ozon-Belastung (ca. 2x2 km^2) für jedes Jahr zugeordnet, auf deren Basis die Krankheitslast in Deutschland abgeschätzt werden kann (AP 4).

AP 4: Quantifizierung der Krankheitslast

AP 4 beinhaltet entsprechend der Leistungsbeschreibung die Quantifizierung der Krankheitslast verursacht durch Ozon für die identifizierten Gesundheitsendpunkte. In AP 4 werden zunächst die notwendigen Gesundheitsdaten zusammengetragen und – bei ausreichender Datenbasis – die Krankheitslast der in AP 1 identifizierten, durch Ozon verursachten Gesundheitsendpunkte mit dazugehörigen Effektschätzern quantifiziert. Die Methodik orientiert sich an der Methodik der World Health Organization (WHO) (Prüss-Üstün et al. 2003) sowie an Vorarbeiten des UBA. Diesbezüglich sind insbesondere die Arbeiten von Schneider et al. (2018), Hornberg et al. (2013) sowie die Schätzungen des UBA zu Feinstaub (Kallweit und Wintermeyer (2013) zu nennen. Als untere Quantifizierungsgrenze für die Hauptanalysen wurde 65 µg/m^3 gewählt. Dieser Wert entspricht in etwa dem 5. Perzentil der Ozon- bzw. dem 2.5 Perzentil der Sommerozon-Exposition in der „American Cancer Society Study II“ (Turner et al. 2016), der bereits in früheren Krankheitslast-Studien als untere Quantifizierungsgrenze verwendet wurde (Malley et al. 2017). Zudem entspricht dieser Wert in etwa dem Erwartungswert bzw. Median der Gleichverteilung, die in der Global Burden of Disease (GBD)-Studie als theoretisches Minimum angenommen wird.

AP 5: Unsicherheiten und Szenarioanalysen

AP 5 enthält laut Leistungsbeschreibung die „Diskussion der Unsicherheiten der Expositions- und Krankheitslastschätzung einschließlich Szenarioanalysen“ (UBA 2018).

Die Analyse von Unsicherheiten erfolgt sowohl qualitativ als auch quantitativ. Dargelegt werden alle im Projekt getroffenen Annahmen, weshalb AP 5 auf allen Projektebenen angesiedelt ist. Im Diskussionskapitel werden quantitative Sensitivitätsbetrachtungen und Szenarioanalysen vorgenommen, indem unterschiedliche Annahmen zur Anwendung kommen. Beispielsweise verdeutlicht die Verwendung unterschiedlicher Effektschätzer je Expositions-Wirkungszusammenhang die Sensitivität, die Robustheit und Belastbarkeit der Ergebnisse. Auch die Berücksichtigung von Konfidenzintervallen ist Inhalt des AP.

Ergebnisse

Ergebnisse aus AP 1 (Literaturrecherche)

Die Literaturrecherche basiert auf Übersichtsarbeiten relevanter Institute und wurde durch eine systematische Recherche aktueller peer-reviewed Literatur ergänzt.

Die systematische Literaturrecherche beinhaltet drei Recherchestränge:

A. Übersichtsarbeiten relevanter Institute

B. Umbrella Review

C. Systematic Mapping

Die Recherche nach Übersichtsarbeiten relevanter Institute ergab, dass die WHO und die amerikanische Umweltbehörde U.S. EPA führend bei der Bereitstellung von Übersichtsarbeiten zu luftschadstoffassoziierten Gesundheitsendpunkten sind. Zusammenfassend lässt sich auf Grundlage dieser Berichte schlussfolgern, dass die Evidenz von respiratorischen Gesundheitsendpunkten durch kurzzeitige Ozonexposition am besten belegt ist und auf dieser Grundlage Empfehlungen, wie Leitwerte der WHO, und Schätzungen für Maßnahmen der Luftreinhaltung abgeleitet wurden.

Das Rechercheprotokoll der Recherchestränge B (Umbrella Reviews) und C (Systematic Mapping) ist seit dem 24.04.2019 im International Prospective Register of Systematic Reviews (PROSPERO) unter der Registrierungsnummer CRD42019123064 (Zhao et al. 2019) registriert und kann dort frei zugänglich abgerufen werden (https://www.crd.york.ac.uk/prospero). Entsprechend den PRISMA-Kriterien ist es üblich, Recherchen für systematische Reviews mindestens anhand von zwei Literaturdatenbanken durchzuführen. Für dieses Vorhaben wurden die Datenbanken PubMed und Web of Science (WoS) ausgewählt.

Die WHO empfiehlt, Relative Risiken zur Schätzung der Population Attributable Fraction (PAF) von gepoolten Auswertungen wie Metaanalysen zu verwenden (WHO 2020). Zudem können Metaanalysen auf der höchsten Evidenzstufe angesiedelt werden (Biondi-Zoccai 2016). Deshalb wird im Rahmen dieses Ozon-Projektes ein Schwerpunkt auf Metaanalysen epidemiologischer Studien gelegt, um die Evidenz der Expositions-Endpunkt-Assoziationen bewerten zu können. Als Reviewmethode wird entsprechend das Umbrella Review ausgewählt. Ein Umbrella Review ist ein systematischer Review von systematischen Reviews und Metaanalysen. Umbrella Reviews repräsentieren das höchste Level der Evidenzsynthese, da die aktuell verfügbaren systematischen Reviews und Metaanalysen zusammengeführt werden (Fusar-Poli und Radua 2018). In dem aktuellen Projekt werden im Rahmen des Umbrella Reviews Metaanalysen epidemiologischer Studien sämtlicher (möglicherweise) mit Ozon assoziierten Gesundheitsendpunkte recherchiert. Neben der Datenbankrecherche (PubMed und WoS) wird das Schneeballverfahren angewendet. Im Rahmen des Umbrella Reviews wurden 70 systematische Reviews identifiziert; 47 davon enthielten eine Metaanalyse mit Ozonbezug und wurden anhand der festgelegten Kriterien (aus AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews), Shea et al. 2017) sowie des Projektes „Quantifizierung von umweltbedingten Krankheitslasten aufgrund der Stickstoffdioxid-Exposition in Deutschland“ (im Folgenden als „NO_2-Projekt“ bezeichnet) bewertet. Auf die Ergebnisse des Umbrella Reviews soll in dieser Zusammenfassung nicht weiter eingegangen werden, weil sich alle identifizierten systematischen Reviews auf Kurzzeitexpositionen beziehen, während sich das vorliegende Projekt auf Langzeitexpositionen (Sommerozon und SOMO35) bezieht.

Systematic Maps, Mapping Reviews (Grant und Booth 2009) oder auch Systematic Evidence Maps (SEM) (Wolffe et al. 2019) sind die übersichtliche Darstellung des Forschungsstandes eines breiten Forschungsfeldes (Miake-Lye et al.2016). „Vorhandene und fehlende Evidenz für medizinische Fragestellungen werden in ihrer Quantität und unter Darstellung von (Studien-) Charakteristika systematisch“ abgebildet (Schmucker et al. 2013, S. 1391). Diese neuartige Reviewform (Miake-Lye et al. 2016) unterscheidet sich von klassischen systematischen Literaturreviews, indem die Evidenz als Ganzes dargestellt wird, und sie sich nicht auf einen im systematischen Review begrenzten Geltungsbereich bezieht. SEMs werden derzeit international umfangreich angewendet (Schmucker et al. 2013). Die Methode des Systematic Mappings wird im Rahmen des Ozon-Projektes verwendet, um die beiden folgenden Ziele zu erreichen: Das erste Ziel des Systematic Mappings ist die Beurteilung der biologischen Plausibilität der Gesundheitsendpunkte, die auf Grund vorhandener Metaanalysen epidemiologischer Studien mit stärkster Evidenz bewertet wurden. Hierfür werden experimentelle Studien (tierexperimentelle und mechanistische/in vitro-Studien) im Rahmen des Systematic Mappings recherchiert und übersichtlich zusammengestellt. Neueste Empfehlungen zu Systematischen Reviews fordern die Prüfung der biologischen Plausibilität (NTP 2015), was somit in dem aktuellen Projekt gewährleistet wird.

Das zweite Ziel des Systematic Mappings ist die Recherche aktueller epidemiologischer Studien seit Publikation der letzten Metaanalyse zu dem entsprechenden Endpunkt. Dabei handelt es sich ausschließlich um Originalarbeiten und nicht um Reviews oder Metaanalysen, die bereits im Umbrella Review eingeschlossen wurden. Die Ergebnisse der aktuellen Originalarbeiten werden ergänzend zu der qualitativen Beschreibung der Evidenz des Endpunktes herangezogen. Außerdem sollen Effektschätzer extrahiert werden, die u. U. zur Krankheitslastschätzung herangezogen werden können.

Die Prüfung der biologischen Plausibilität wird für die Gesundheitsendpunkte mit starker Evidenz durchgeführt. Unabhängig von der Evidenzprüfung wurde der Gesundheitsendpunkt Chronic Obstructive Pulmonary Diseases (COPD, chronisch obstruktive Lungenerkrankung) frühzeitig für das Systematic Mapping festgelegt. Grund für diese Vorauswahl ist, dass die derzeit größte Krankheitslaststudie COPD-Mortalität als einzigen ozonbedingten Gesundheitsendpunkt einbezieht (GBD 2017 Risk Factor Collaborators 2018). Die Studie zu Global Burden of Disease (GBD) hat COPD als biologisch plausiblen Endpunkt von Ozon beurteilt. Allerdings erfolgte diese Beurteilung allein auf Grundlage epidemiologischer Studien (GBD 2017 Risk Factor Collaborators 2018, Anhang 1, S. 22). Die Beurteilung auf Grundlage experimenteller Studien für COPD und mindestens eines weiteren Gesundheitsendpunktes erfolgt erstmals im Rahmen dieses Projekts. Nach Ausschluss von Duplikaten ergab das SEM für COPD 368 Treffer.

Für die Krankheitslastberechnungen dieses Vorhabens wurden Effektschätzer für die Ozon-Endpunkt-Paare mit starker Evidenz auf Grundlage epidemiologischer Studien und der biologischen Plausibilität auf Grundlage experimenteller Studien extrahiert:

Bei der Auswahl der Effektschätzer für die Berechnung der Krankheitslast wurde folgendermaßen vorgegangen: Wenn mehrere Effektschätzer aus einer Studie publiziert wurden, wurde jener Effektschätzer ausgewählt, dem die längste Beobachtungszeit zu Grunde liegt (und der damit auch in der Regel zuletzt publiziert wurde), was dem üblichen Vorgehen bei Metaanalysen von Ergebnissen systematischer Reviews entspricht. Allerdings wurden zusätzliche Sensitivitätsanalysen durchgeführt.

Im Ergebnis der umfangreichen systematischen Recherchen dieses Projektes wurden weitere mögliche Gesundheitsendpunkte in Folge langzeitiger Ozonexpositionen, wie die Gesamtmortalität und kardiovaskuläre Mortalität und Morbidität sowie metabolische Effekte wie zum Beispiel Diabetes Mellitus, außerdem Parkinson-Syndrom und Indikatoren für reproduktive Gesundheit einer Prüfung unterzogen. Im Ergebnis auf Grundlage epidemiologischer Studien sowie der biologischen Plausibilität stellten sich ausschließlich die respiratorische Mortalität sowie die COPD-Mortalität als Untergruppe der respiratorischen Mortalität als kausal mit einer langfristigen Exposition gegenüber Ozon assoziiert heraus. Andere Krankheitsentitäten erwiesen sich im Zusammenhang mit langfristigen Ozonexpositionen entweder als biologisch nicht ausreichend plausibel abgesichert (kardiovaskuläre Erkrankungen, metabolische und neurologische Erkrankungen) oder epidemiologisch nicht ausreichend untersucht.

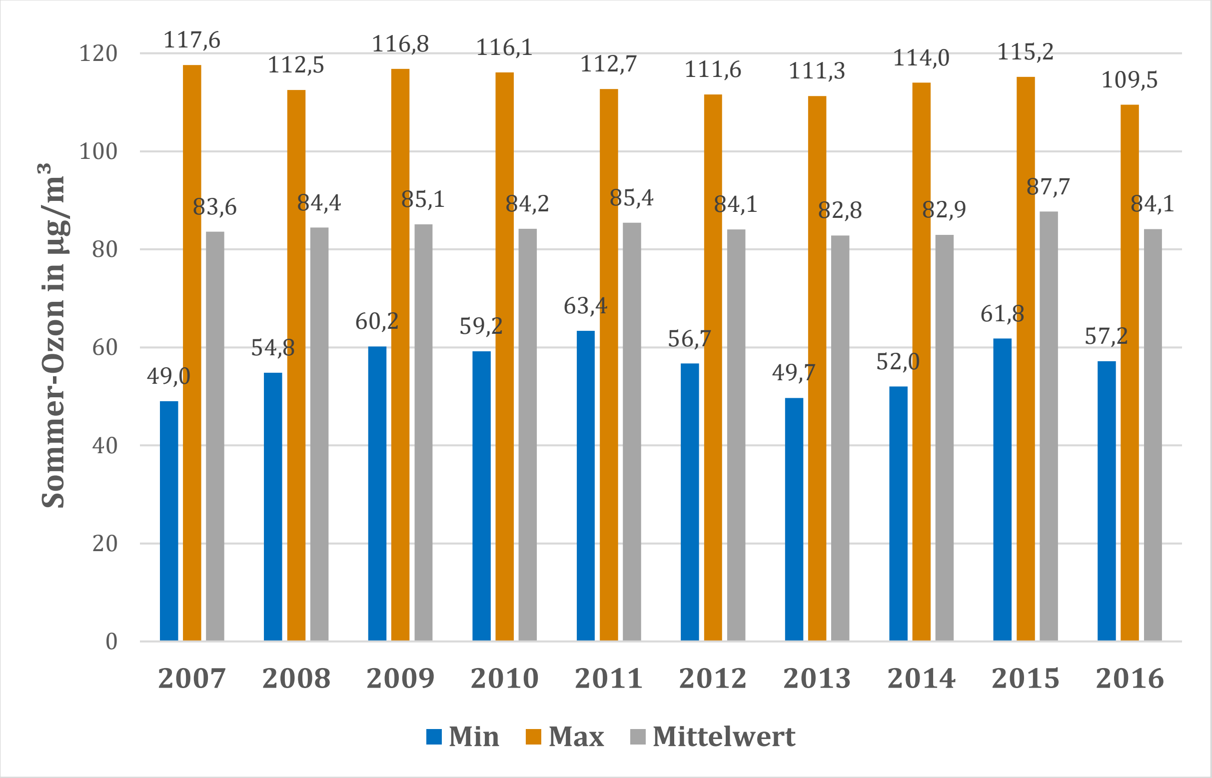
Ergebnisse aus AP 2 und AP 3: Expositionsschätzung

Grundlage für die deutschlandweite Ermittlung der Ozon-Exposition sind flächendeckende Daten der räumlichen Verteilung der Ozon-Hintergrundwerte in der Außenluft. Für die Berechnung genutzt werden die Daten der Jahre 2007 bis 2016, die das Belastungsniveau im ländlichen und städtischen Hintergrund in einer räumlichen Auflösung von ca. 2 x 2 km^2 abbilden. Die Daten wurden anhand des chemischen Transportmodells REM/CALGRID (RCG) generiert, die mit Ozon-Messdaten mittels der Methodik der Optimalen Interpolation (OI) kombiniert wurden (Flemming et al. 2004).

Für das Projekt wurden zwei Expositionsschätzer vorgeschlagen - SOMO35, der die „jährliche Summe über die täglichen Maxima der 8-stündigen gleitenden Mittelwerte angibt, die 35 ppb überschreiten“ (OECD 2008, S. 194) und die mittlere maximale 8-Stundenkonzentration in den Sommermonaten, nachfolgend Sommer-Ozon genannt. Da sich fast alle epidemiologischen Studien auf Sommer-Ozon bezogen, kann der SOMO35 nur bedingt für Krankheitslaststudien herangezogen werden.

Abbildung A 1 zeigt die Verteilung des Sommer-Ozons für die Jahre 2007 bis 2016. Dabei ist kein Trend über den Beobachtungszeitraum erkennbar.

Abbildung A 1: Mittlere, minimale und maximale Sommer-Ozon-Konzentrationen in Deutschland für den Zeitraum 2007 bis 2016



Abkürzungen: µg/m³, Mikrogramm pro Kubikmeter; Max, maximaler Wert; Min, minimaler Wert; Mittelwert, jeweils bezogen auf das Sommer-Ozon-Flächenmittel ermittelt aus Daten der Hintergrundmessstationen : Mittelwert der täglichen Maxima der gleitenden 8-Stundenmittelwerte in den Sommermonaten April bis September

Quelle: Eigene Darstellung der vom UBA bereitgestellten Daten

AP 4 und AP 5: Quantifizierung der Krankheitslast und Unsicherheits- und Szenarioanalysen

In Tabelle A 1 sind die Ergebnisse zur respiratorischen Krankheitslast (ICD-10 Kodierung J00-J99) durch Langzeitexposition gegenüber Sommer-Ozon in den Jahren 2007 bis 2016 dargestellt. Als Expositions-Wirkungsfunktion wurde ein mittels Metaanalyse zusammengefasster Schätzer aus den Studien von Lim et al. (2019), Kazemiparkouhi et al. (2019), Weichenthal et al. (2017), Turner et al. (2016), Bentayeb et al. (2015) und Lipsett et al. (2011) verwendet; basierend auf dem Altersbereich der Studienpopulationen wurde als Altersbereich 30 Jahre und älter festgelegt. Die Ergebnisse umfassen den sogenannten attributablen Anteil, also den Anteil der Krankheitslast, der mittels statistischer Verfahren auf Ozon zurückgeführt werden kann, sowie verlorene gesunde Lebensjahre in absoluten Zahlen und in Form einer Rate (pro 100.000 Einwohnenden).

Die Ergebnisse beziehen sich auf die deutsche Bevölkerung. Dabei ist zu beachten, dass die verlorenen Lebensjahre nicht gleichverteilt auf alle Einwohnenenden sind, sondern dass einige Einwohnende mehr Lebensjahre als andere verlieren.

Tabelle A 1: Respiratorische Krankheitslast (ab einem Alter von 30 Jahren) durch Langzeitexposition gegenüber Sommer-Ozon in Deutschland – 2007 bis 2016; untere Quantifizierungsgrenze 65 µg/m³

Jahr	2007	2008	2009	2010	2011
Attributabler Anteil in % (95 % KI)	4,05 (2,56-5,67)	4,26 (2,69-5,96)	4,50 (2,85-6,29)	4,34 (2,75-6,07)	4,87 (3,09-6,81)
Years of Life Lost (YLL) (95 % KI)	21.822 (13.790-30.540)	23.395 (14.793-32.720)	26.437 (16.728-36.949)	24.768 (16.667-34.627)	27.699 (17.540-38.678)
YLL je 100.000 Einwohnende (95 % KI)	26,53 (16,76-37,12)	28,49 (18,01-39,84)	32,29 (20,43-45,13)	30,29 (19,16-42,35)	34,50 (21,85-48,18)
Jahr	**2012**	**2013**	**2014**	**2015**	**2016**
Attributabler Anteil in % (95 % KI)	4,34 (2,74-6,07)	4,03 (2,55-5,64)	4,10 (2,59-5,74)	5,49 (3,48-7,66)	4,43 (2,80-6,19)
Years of Life Lost (YLL) (95 % KI)	24.169 (15.283-33.803)	24.735 (15.637-34.604)	22.770 (14.393-31.857)	35.481 (22.488-49.497)	27.257 (17.243-38.103)
YLL je 100.000 Einwohnende (95 % KI)	30,05 (19,00-42,03)	30,67 (19,39-42,91)	28,12 (17,77-39,34)	43,44 (27,53-60,59)	33,10 (20,94-46,27)

Abkürzungen: KI, Konfidenzintervall; **gepoolter Schätzer** der Studien Lim et al. 2019, Kazemiparkouhi et al. 2019, Weichenthal et al. 2017, Turner et al. 2016, Bentayeb et al. 2015 und Lipsett et al. 2011: **1,024 (95 % KI: 1,015-1,034) pro 10 µg/m³**

Der attributable Anteil der respiratorischen Krankheitslast aufgrund von Sommer-Ozon lag im Bereich von 4,03 % (KI: 2,55-5,64) (Jahr 2013) bis 5,49 % (KI: 3,48-7,66) (Jahr 2015). Insgesamt ist im Zeitraum 2007 bis 2016 keine eindeutige Tendenz in der Krankheitslast zu erkennen – im Beobachtungszeitraum von zehn Jahren war eine Schwankung der Krankheitslast von mehr als einem Drittel von Jahr zu Jahr zu beobachten, ähnlich dem Verlauf der Ozon-Konzentrationen. Ein Vergleich der Ergebnisse mit jenen nach Adjustierung für $PM_{2.5}$ und NO_2 zeigt etwas niedrigere Krankheitslasten bei Adjustierung für diese Luftschadstoffe.

In Tabelle A 2 sind die Ergebnisse zur COPD-Krankheitslast (ICD-10 Kodierung J40-J44) durch Langzeitexposition gegenüber Sommer-Ozon in den Jahren 2007 bis 2016 dargestellt. Der attributable Anteil liegt im Bereich von 6,11 % (Jahr 2013) bis 8,29 % (Jahr 2015), die verlorenen Lebensjahre pro 100.000 Einwohnende im Bereich von 18,33 YLL (Konfidenzintervall, KI: 14,02-22,08) (Jahr 2007) bis 35,77 YLL (KI: 27,45-42,98) (Jahr 2015). Ähnlich zur respiratorischen Krankheitslast ist auch hier keine eindeutige Tendenz in der Krankheitslast über den Beobachtungszeitraum zu erkennen.

Tabelle A 2: COPD-Krankheitslast (ab einem Alter von 30 Jahren) durch Langzeitexposition gegenüber Sommer-Ozon in Deutschland – 2007 bis 2016; untere Quantifizierungsgrenze 65 µg/m^3

Jahr	2007	2008	2009	2010	2011
Attributabler Anteil in % (95 % KI)	6,15 (4,70-7,40)	6,46 (4,94-7,78)	6,81 (5,22-8,20)	6,58 (5,04-7,92)	7,37 (5,65-8,87)
Years of Life Lost (YLL) (95 % KI)	15.078 (11.535-18.162)	16.097 (12.323-19.380)	19.076 (14.612-22.953)	18.763 (14.369-22.583)	21.243 (16.285-25.543)
YLL je 100.000 Einwohnende (95 % KI)	18,33 (14,02-22,08)	19,60 (15,01-23,60)	23,30 (17,85-28,03)	22,95 (17,57-27,62)	26,46 (20,29-31,82)
Jahr	**2012**	**2013**	**2014**	**2015**	**2016**
Attributabler Anteil in % (95 % KI)	6,58 (5,04-7,92)	6,11 (4,68-7,36)	6,23 (4,76-7,50)	8,29 (6,36-9,96)	6,71 (5,14-8,07)
Years of Life Lost (YLL) (95 % KI)	19.006 (14.549-22.881)	19.751 (15.116-23.784)	18.828 (14.408-22.673)	29.222 (22.421-35.111)	22.993 (17.609-27.672)
YLL je 100.000 Einwohnende (95 % KI)	23,63 (18,09-28,45)	24,49 (18,74-29,49)	23,25 (17,79-28,00)	35,77 (27,45-42,98)	27,92 (21,38-33,60)

Abkürzungen: KI, Konfidenzintervall; **gepoolter Schätzer** der Studien Lim et al. 2019, Kazemiparkouhi et al. 2019, und Turner et al. 2016: **1,037 (95 % KI: 1,028, 1,045) pro 10 µg/m^3**

Zusätzlich wurde eine Schätzung der Krankheitslasten durch Sommer-Ozon basierend auf für Feinstaub und NO_2 adjustierten Effektschätzern durchgeführt. Während sich die respiratorische Krankheitslast bei Verwendung der Expositions-Wirkungs-Funktionen nach Adjustierung für Feinstaub und NO_2 etwas verringerte, wird die Krankheitslast für COPD sogar höher.

Im Hinblick auf den zweiten Ozon-Belastungsindikator, den SOMO35, konnte nur die respiratorische Krankheitslast auf der Basis eines einzigen, jedoch etwas älteren Risikoschätzers aus dem Jahr 2009 (Jerrett et al. 2009) berechnet werden. Ein Vergleich mit den aktuellen Krankheitslastschätzungen für Sommer-Ozon ist daher nur bedingt aussagefähig.

In Szenarioanalysen wurden neben 65 µg/m^3 als untere Quantifizierungsgrenze auch eine Grenze von 71 µg/m^3 für respiratorische und COPD-Krankheitslast betrachtet. Auch unter Verwendung der konservativeren unteren Quantifizierungsgrenze von 71 µg/m^3 zeigten sich für die respiratorische Krankheitslast noch Sommer-ozonbedingte YLLs pro 100.000 Einwohnende im Bereich von 17,72 (95 %-Konfidenzintervall, KI: 11,16-24,88) bis 32,72 (95 % KI: 20,68-45,78). Für COPD-Krankheitslast lagen die YLLs pro 100.000 Einwohnende im Bereich von 12,29 (95 % KI: 9,38-14,85) bis 27,06 (95 % KI: 20,70-32,59). Die Breite der Konfidenzintervalle wird maßgeblich durch die Wahl der unteren Quantifizierungsgrenze bestimmt. Dabei wird für einen variierenden Teil der Bevölkerung kein gesundheitliches Risiko durch Sommer-Ozon und somit auch keine Variation des Effektes – in Form des KI der EWF – angenommen. So wird z. B. Bei einer unteren Quantifizierungsgrenze von 65 µg/m^3 für ca. 0,01 % (Jahr 2015) bis 1,10 % (Jahr 2007) der Einwohnenden Deutschlands wird z. B. kein gesundheitliches Risiko angenommen – bei einer unteren Quantifizierungsgrenze von 71 µg/m^3 ist dies für ca. 0,03 % (Jahr 2015) bis 4,49 % (Jahr 2007) der Bevölkerung der Fall.

Neben den Schwankungen der Krankheitslasten durch Ozon von Jahr zu Jahr, die sich aus den Veränderungen der Ozonkonzentrationen ergeben, spielen die zu Grunde gelegten Risikoschätzer die entscheidende Rolle bei der Quantifizierung von Unsicherheiten. Hinzu kommt die qualitative Einschätzung der Unsicherheiten durch die nicht abschließend beantwortbare Frage nach der Übertragbarkeit der Risikoschätzer, die überwiegend nordamerikanischen Studien entstammen, auf die Situation in Deutschland. Weitere Faktoren der Unsicherheit wie die Fehler bei der Fortschreibung der Bevölkerung Deutschlands nach dem Zensus und den generischen Unsicherheiten in der Todesursachenstatistik werden als weniger bedeutsam eingestuft.

Diskussion und Schlussfolgerung

Den globalen Studien, die die durch Langzeitexpositionen mit Ozon verursachte Krankheitslast quantifiziert haben, liegt die von der WHO entwickelte Methode zur Schätzung umweltbedingter Krankheitslasten zu Grunde (Prüss-Üstün et al. 2003). Allerdings unterscheiden sich diese Studien deutlich in den Eingangsdaten. Fast alle Studien beziehen sich auf den Effektschätzer, der von Jerrett et al. im Jahr 2009 publiziert wurde. Seit der wegweisenden Publikation von Jerrett et al. (2009) sind einige weitere Langzeitstudien publiziert worden, die im Rahmen dieses Vorhabens erstmals einer Krankheitslastberechnung zu Grunde gelegt werden konnten. Ein Vergleich der Krankheitslastschätzungen zwischen den verschiedenen Studien ist wegen der unterschiedlich verwendeten Eingangsdaten nur bei strikter Beachtung der Unsicherheiten sinnvoll.

Im Oktober 2020 wurde die letzte Krankheitslastschätzung durch langfristige Ozonexpositionen ausschließlich auf die COPD-Mortalität als Ergebnis der GBD-Studie publiziert (GBD 2019 Risk Factors Collaborators 2020). Diesen Schätzungen lag der aus drei Kohorten gemittelte

Risikoschätzer von 1,06 (95 % KI: 1,02-1,10) für einen Anstieg von 10 ppb Sommer-Ozon zu Grunde (Metaanalyse mit inverser Varianz). Die Schätzung basiert auf drei Kohorten (American Cancer Society (ACS), Canadian Census Health and Environment Cohort (CanCHEC), Clinical Practice Research Datalink (CPRD)), (Supplement to: GBD 2019 Risk Factors Collaborators 2020, Carey et al. 2013, Turner et al. 2016). Für das Jahr 2016 wurden für Deutschland 43,05 ozonbedingte YLLs pro 100 000 Personen (95 % KI: 18,14-74,06) publiziert (Ergebnisse für Deutschland unter: http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2019-permalink/46cfcd25e4b103a1db1882f054997e67). Diese Zahlen liegen etwas über den im vorliegenden Projekt geschätzten YLLs – 18,33 YLL (95 % KI: 14,02-22,08) im Jahr 2007 bis 35,77 YLL (95 % KI: 27,45-42,98) im Jahr 2015. Die folgenden Faktoren können die Abweichung erklären: In der GBD-Studie wird eine etwas höhere Ozonexposition angenommen als in der aktuellen Studie geschätzt wurde. Die Schätzung der GBD-Studie beruht auf einem Raster von 11 x 11 km, während in der aktuellen Studie eine hohe Auflösung von 2 x 2 km verwendet werden konnte. Darüber hinaus ist die in der GBD-Studie verwendete standardisierte Lebenserwartung höher als die in Deutschland dokumentierte Lebenserwartung. Außerdem wurde in der GBD-Studie die Krankheitslast für alle Altersgruppen ab 25 Jahren geschätzt, während die aktuelle Studie die untere Altersgrenze auf 30 Jahre festgelegt hat. Vernachlässigbare Faktoren, die die Abweichung nicht oder in sehr geringem Ausmaß beeinflusst haben könnten, sind leichte Abweichungen bei der Höhe der verwendeten Risikoschätzer sowie leichte Abweichungen bei den verwendeten ICD-10-Kodierungen und unteren Quantifizierungsgrenzen.

Interessant sind die erstmals vorgelegten Schätzungen für die respiratorische Krankheitslast durch Ozon, wenn Effektschätzer verwendet werden, die für andere Luftschadstoffe wie $PM_{2.5}$ und NO_2, sowie für die Temperatur adjustiert wurden. Dabei zeigten sich zwar geringfügig niedrigere Schätzer, allerdings deuten diese Ergebnisse auf einen von anderen Luftschadstoffen weitestgehend unabhängigen Effekt von Ozon auf die respiratorische Krankheitslast hin. Dabei ist jedoch zu berücksichtigen, dass die Höhe der Ozonkonzentrationen und der Schadstoffmix in den USA (fast alle berücksichtigten Studien wurde dort durchgeführt) nicht unbedingt mit dem in Deutschland vergleichbar sind, u. a. wegen einer unterschiedlichen Emittentenstruktur, anderer klimatischer Verhältnisse und damit atmosphärischer Umwandlungsprozesse. Des Weiteren bedarf es einer Interpretation und Diskussion, weshalb die respiratorische Krankheitslast durch Ozon (geringfügig) niedriger ist im Vergleich zur COPD-Krankheitslast. Dieses Ergebnis scheint auf den ersten Blick nicht plausibel zu sein, weil die COPD-Mortalität eine Untergruppe der respiratorischen Mortalität ist. Allerdings liegen den Berechnungen der respiratorischen und der COPD-Krankheitslast unterschiedliche Risikoschätzer zu Grunde. Der verwendete Risikoschätzer für die COPD-Krankheitslast ist größer als jener für die respiratorische Krankheitslast und führt allein deswegen auch zu einer höheren Krankheitslast für COPD. Hinzu kommt, dass die gesundheitliche Schadwirkung des Ozons sich spezifisch auf die COPD nachweisen lässt und die Wirkungen auf die respiratorische Krankheitslast vor allem durch die COPD bedingt sind. Die respiratorische Mortalität setzt sich überwiegend zusammen aus der COPD-Mortalität und der Mortalität aufgrund von Pneumonie. Da Letztere weniger stark mit Ozonwirkungen assoziiert ist, werden die gesundheitlichen Effekte des Ozons abgeschwächt. Zuallerletzt sei angemerkt, dass sich Krankheitslasten aus verschiedenen Modellen nicht einfach addieren oder subtrahieren lassen. Insofern sind die vorgestellten Ergebnisse bei genauerer Betrachtung nicht unplausibel.

Die European Environmental Agency (EEA 2019) hat unter Verwendung des SOMO35 die ozonbedingten YLLs und attributablen Todesfälle für Deutschland bestimmt. Es resultierten 24.400

YLL (30 YLL pro 100.000 Einwohnenden). Ein Vergleich mit den Ergebnissen dieses Projektes ist auch hier nur mit Vorsicht möglich, weil unterschiedliche Gesundheitsendpunkte und unterschiedliche Expositionen zu Grunde gelegt wurden (EEA: Gesamtmortalität und Kurzzeiteffekte, vorliegende Studie: Respiratorische Mortalität und Langzeiteffekte). In der vorliegenden Studie wurden 7.604 YLL (9,23 YLL pro 100.000 Einwohnenden) bestimmt. Auf den Vergleich mit den Ergebnissen des VegAS-Projektes (Hornberg et al. 2013) wird wegen der noch deutlicher verschiedenen Eingangsdaten (Kurzzeiteffekt-Risiken) verzichtet. Auch sei darauf hingewiesen, dass die Kombination von bevölkerungsgewichteten Langzeitexpositionen mit Effektschätzern aus Kurzzeitexpositions-Studien in methodischer Hinsicht Fragen aufwirft.

Angesichts der Komplexität der hier verwendeten Modelle und der Unsicherheiten der Eingangsdaten ist eine Darstellung der Stärken und Schwächen dieses Projektes zwingend notwendig.

Dieses Vorhaben hat eine Reihe von unstrittigen Stärken. Dazu zählen:

- Die Quantifizierung der durch Ozon verursachten Krankheitslast erfolgt nach dem von der WHO entwickelten Konzept der umweltbedingten Krankheitslast (Prüss-Üstün et al. 2003). Wir betrachten die Anwendung dieses Modells als Stärke, weil es sich zum einschlägigen Standard entwickelt hat und die ohnehin vorhandene Heterogenität zwischen verschiedenen Krankheitslaststudien reduziert. Dennoch sei an die Diskussion der Limitierungen dieses Vorgehens erinnert, wie sie in Hornberg et al. (2013) und Srebotnjak et al. (2015) diskutiert wurden.
- Das systematische Umbrella Review und insbesondere die drei Systematic Mappings stellen ein modernes Konzept dar, um zahlreiche Studienergebnisse unter Einbeziehung experimenteller Studien im Hinblick auf die Evidenz für eine zu Grunde liegende Kausalität beurteilen zu können.
- Die Verwendung der aktuellen Effektschätzer der American Cancer Society (ACS, Turner et al. 2016) und der Canadian Census Health and Environment Cohort (CanCHEC, Weichenthal et al. 2017) sowie weiterer erstmals publizierter Effektschätzer wird als zusätzliche Stärke dieser Studie angesehen.
- Die quantitative Zusammenfassung der Effektschätzer aus verschiedenen Studien (Metaanalysen unter Einbeziehung der Konfidenzintervalle der Einzelstudien) stellt ebenfalls eine Stärke dieses Vorhabens dar, denn fast alle früheren Krankheitslaststudien zu Ozon beziehen sich nur auf einen einzigen Effektschätzer (von Jerrett et al. 2009), was in der Literatur durchaus kritisch angemerkt wurde (Prueitt und Goodman 2011).
- Es wurden Effektschätzer, die für Feinstaub, NO_2 und Temperatur adjustiert wurden, zur Schätzung der Krankheitslast durch Ozon verwendet. Das ist besonders wichtig, weil seit Jahren die Anwendung von Schätzern aus „single-pollutant“ Modellen bemängelt wird, vielfach ohne Abhilfe zu schaffen.

- Den vom Auftraggeber vorgegebenen Titel zur Krankheitslast, die durch Ozon verursacht wird und den daraus abgeleiteten Fokus auf kausalen Wirkungen bewerten wir als Stärke des Vorhabens, weil diese Fokussierung eine Diskussion der Kausalität bei Assoziationsstudien erübrigt.
- Die Auflösung der flächenbezogenen Ozonkonzentration für ein Raster von 2 km x 2 km in dieser Studie ist höher als in allen anderen vergleichbaren Studien.
- Die zahlreichen Sensitivitätsanalysen unter Ein- bzw. Ausschluss einzelner Studien zu den Effektschätzern sowie die zwei Belastungsindikatoren zu Sommer-Ozon und SOMO35 erachten wir ferner als Stärken, weil dadurch die Konsistenz und Robustheit der Ergebnisse eingeschätzt werden konnte.

Dieses Vorhaben hat allerdings auch eine Reihe von Limitierungen, die im Nachfolgenden kurz benannt werden.

- Die bei der umweltbedingten Krankheitslast geschätzten Summenmaße stellen Kennzahlen für die Bevölkerungsgesundheit dar. Die Ergebnisse von Studien zum Environmental Burden of Disease (EBD) sind daher ausschließlich für die Ableitung von Aussagen auf Bevölkerungsebene zu verwenden. Informationen zum Gesundheitszustand einzelner Individuen können aus EBD-Studien nicht abgeleitet werden. Darüber hinaus handelt es sich um Schätzer, die durch Modellberechnungen ermittelt werden. In derartigen Modellberechnungen müssen verschiedene Annahmen getroffen werden, wie zum Beispiel über die verwendete Expositions-Wirkungsfunktion oder die Restlebenserwartung zum Todeszeitpunkt.
- Generell gilt, dass die Unsicherheiten der Ergebnisse einer Krankheitslaststudie nicht kleiner sein können als die Unsicherheiten der Eingangsdaten. Insofern sind die Unsicherheiten der Eingangsdaten zu benennen.
- Die Effektschätzer entstammen überwiegend großen nordamerikanischen Studien und die Übertragbarkeit auf deutsche Verhältnisse ist eine erforderliche pragmatische Vorgehensweise, weil keine einschlägigen Daten aus Deutschland bzw. Europa zur Verfügung stehen. Damit sind einige unwägbare Unsicherheiten verbunden.
- Im Hinblick auf die berechnete Exposition mit Ozon muss deutlich darauf hingewiesen werden, dass es sich dabei lediglich um die modellierte Ozonkonzentration in einem bestimmten (kleinräumigen) Raster über Deutschland handelt. Das ist insbesondere wegen der unterschiedlichen Aufenthaltsdauern von Personen im Freien eine stark vereinfachte (wenn auch übliche) Vorgehensweise, um eine Exposition abzuschätzen.
- Die Unsicherheitsbereiche der Krankheitslastschätzungen durch Ozon, wie sie zum Beispiel durch die Konfidenzintervalle sichtbar werden, sind sehr groß. Deswegen ist explizit von einer unkritischen Verwendung des Punktschätzers ohne Angabe des Konfidenzintervalls zu warnen.

- Wegen der deutlichen methodischen Unterschiede zur Berechnung der Krankheitslasten durch die Luftschadstoffe Feinstaub, NO_2 und Ozon in Deutschland ist ein direkter Vergleich nur eingeschränkt möglich.
- Die über die Sommermonate gemittelten Ozonkonzentrationen und auch der SOMO35 können mögliche Effekte von Spitzenbelastungen nicht adäquat abbilden.
- Bei der Interpretation der Ergebnisse zu den verlorenen Lebensjahren ist zu berücksichtigen, dass die verlorenen Lebensjahre nicht gleich verteilt über alle Altersgruppen sind.

Trotz der inhärenten Unsicherheiten und Limitierungen halten wir die Ergebnisse dieses Vorhabens insgesamt für belastbar, sofern sich die Zusammenfassungen und Kurzberichte nicht auf die Punktschätzer beschränken und stets die Konfidenzintervalle als Maß der Unsicherheit gleichfalls angegeben werden.

Zusammenfassend ist aus dem vorliegenden Projekt Folgendes zu schließen:

a. Langzeitexpositionen mit Ozon tragen auch in der deutschen Allgemeinbevölkerung zur Krankheitslast bei. Angesichts einer möglichen Zunahme der Ozonkonzentration (infolge des Klimawandels) sind intensivere Forschungen zu gesundheitlichen Wirkungen des Ozons erforderlich.

b. Die Schätzungen der Krankheitslast durch Ozon schwanken stark von Jahr zu Jahr wegen der Variationen der Ozonkonzentrationen von Jahr zu Jahr. Die Berechnung der Krankheitslast für nur ein einziges beliebig ausgewähltes Jahr ist nicht zu empfehlen.

c. Auch ein Beobachtungszeitraum von 10 Jahren ist zu kurz, um Trends der Ozonkonzentrationen und damit auch in der Krankheitslast zu quantifizieren.

d. Für Europa und speziell für Deutschland gibt es einen Mangel an verlässlichen epidemiologischen Daten zu Langzeitwirkungen des Ozons, der durch Sekundärdatenanalysen im Rahmen bereits durchgeführter Projekte und durch neue Kohortenstudien kompensiert werden sollte.

e. Interaktionen der langzeitigen Ozonexposition mit flüchtigen organischen Verbindungen, ultrafeinen Partikeln und Grünflächen sind bislang im Hinblick auf gesundheitliche Wirkungen auch international nicht erforscht. Das ist ein anspruchsvolles und innovatives Forschungsfeld.

f. Es fehlen belastbare epidemiologische Ergebnisse zu langzeitigen Ozonexpositionen und dem Auftreten von Asthma und Heuschnupfen.

Summary

Background

The German Environment Agency (UBA) has initiated this project "Quantification of the burden of disease caused by ozone exposure in Germany for the years 2007-2016". The background of the call for proposals is the temporal change of ozone concentrations in Germany, which can be described by a slightly increasing mean ozone concentration with a simultaneous slight decrease of peak concentrations (1995-2017) (UBA 2019b). Moreover, due to climate change, further temporal changes in ozone concentrations in Germany can also be expected. In addition, the health effects of ground-level ozone compared to particulate matter and NO_2 have been neglected in research over the last 20-30 years (Zhao et al. 2019), however the Organisation for Economic Co-operation and Development (OECD) considers ground-level ozone to be the most important health risk factors in outdoor air besides particulate matter (OECD 2012).

Ground-level ozone

The trace gas ozone is a naturally occurring component of air and is present in gaseous form under normal atmospheric conditions (Bavarian State Office for the Environment, LfU 2018). As a molecule consisting of three oxygen atoms (molecular formula O_3), ozone is highly reactive and one of the strongest oxidizing agents (Zhang et al. 2019). Ozone is not emitted directly but is formed as a secondary air constituent through complex photochemical reactions in the presence of precursors and at higher temperatures (Lumb 2017, U.S. EPA 2013). A distinction must be made between "good" stratospheric and "bad" tropospheric ozone (Zhang et al. 2019). Stratospheric ozone accounts for approx. 90% of the ozone present and, as the ozone layer that protects life on earth, absorbs a large proportion of harmful ultraviolet (UV) radiation. Tropospheric, so-called ground-level ozone, on the other hand, irritates and damages cells of plants, animals, and humans. Ground-level ozone originates to a small extent from the upper layers of the atmosphere, but it is largely formed by UV radiation from the precursors nitrogen oxide (NO_x), carbon monoxide (CO) and volatile organic compounds (VOCs) of natural and anthropogenic origin, especially in spring when temperatures rise and solar radiation increases (Zhang et al. 2019, LfU 2018).

The current state of knowledge on ground-level ozone and in particular on its health effects is excellently summarized by the recently published expert report of the U.S. Environmental Protection Agency (U.S. EPA) (2020).

According to the pathophysiological responses, respiratory health effects in humans in particular are attributed to short-term exposure to ozone. According to the U.S. EPA (2013), the evidence on the relationship between ozone and cancer is comparatively small. There is also uncertainty in the scientific data on cardiovascular health effects, as there is relatively little knowledge about how ozone affects the cardiovascular system (Zhang et al. 2019). To protect human health, the 1339th BImSchV defines target values that refer to mean concentrations (moving maximum 8-hour mean values). In addition, it is stipulated that the population must be informed and warned in case of high ozone levels (information and alarm thresholds).

Project goals

The main objective of the project is to quantify the burden of disease caused by long-term exposure to ozone for the population in Germany. To this end, the following individual objectives are being pursued:

1. To record the population-related exposure to ozone during the summer months (April to September) and the sum of ozone levels above 35 ppb during one year (SOMO35) in Germany for the years 2007-2016
2. Identification of epidemiological studies on the health effects of ground-level ozone (Umbrella Review) and especially the identification of health outcomes with a causal effect after the inclusion of experimental studies in the systematic reviews (Systematic Mapping).
3. Quantification of the burden of disease caused by ozone in terms of Years lived with Disability (YLD), Years of Life Lost (YLL) and Disability-Adjusted Life Years (DALYs).
4. Estimation of the burden of disease caused by ozone after adjustment for other air pollutants (particulate matter, NO2) and temperature

Methods

The project consists of the following five work packages (WP). WP 1, 2 and 3 form the basis for WP 4. WP 5 has an overarching function and is located in all other WPs. In the course of the project, WP 1 was extended by an increase in project size; WP 2 and 3 were merged.

Work package (WP) 1: Literature search

WP 1 comprises a systematic literature search on the current state of scientific knowledge on the health effects of ozone (morbidity and mortality). A systematic literature search will be conducted to investigate the health effects and the associated effect estimates that describe the relationship between exposure and effect. Morbidity and mortality, short-term and long-term effects, and combination effects (ozone in relation to other air pollutants and temperature) are considered in order to obtain the most comprehensive picture possible of the health effects caused by ozone.

Project extension: Biological plausibility

The project originally planned to review only the epidemiological evidence of possible ozone-related health outcomes in a systematic review. This no longer corresponds to the current status of systematic reviews, where the inclusion of experimental studies is explicitly required (NTP 2015). To strengthen the evidence collected in the ozone project, the project was expanded by the creation of an additional systematic literature review including experimental studies (animal studies and mechanistic/in vitro studies) to test the biological plausibility of selected epidemiologically confirmed health outcomes. By including experimental studies, the causality of the relationship between ozone exposure and the respective health effects, which was proven in epidemiological studies, could be confirmed.

WP 2 and WP 3: Exposure estimation

WP 2 and WP 3 contain the estimation of the area-wide population-weighted ozone exposure in Germany for the period 2007 to 2016 and especially for the summer months and the SOMO35 (annual sum of the daily maxima of the moving 8-hour averages considering the days with ozone values above 35 ppb and 70 µg/m^3 respectively). The population of Germany is assigned a spatially high-resolution ozone load (approximately 2x2 km^2) for each year, on the basis of which the disease burden in Germany can be estimated (WP 4).

WP 4: Quantification of the burden of disease

WP 4 includes the quantification of the burden of disease caused by ozone for the identified health outcomes. In WP 4, the necessary health data will be collected and – if sufficient data is available – the burden of disease for the ozone-induced health outcomes identified in WP 1 will be quantified with corresponding effect estimates. The methodology is based on the methodology of the World Health Organization (WHO) (Prüss-Üstün et al. 2003) as well as on previous research of the UBA. In this respect, the work of Schneider et al. (2018), Hornberg et al. (2013) and the estimates of the UBA on particulate matter (UBA 2019a) are particularly noteworthy. 65 µg/m^3 was chosen as the lower quantification limit for the main analyses. This value corresponds approximately to the 5th percentile of ozone and the 2.5 percentile of summer ozone exposure in the "American Cancer Society Study II" (Turner et al. 2016), which was already used as the lower limit of quantification in earlier disease burden studies (Malley et al. 2017). In addition, this value corresponds approximately to the expected value or median of the equal distribution, which is assumed as the theoretical minimum in the GBD study.

WP 5: Uncertainties and scenario analyses

WP 5 contains the "Discussion of the uncertainties of exposure and disease burden estimation including scenario analyses" (UBA 2018).

The analysis of uncertainties is both qualitative and quantitative. All assumptions made in the project are presented, which is why WP 5 is located at all project levels. In the discussion chapter, quantitative sensitivity considerations and scenario analyses are made by applying different assumptions. For example, the use of different effect estimates per exposure-effect relationship illustrates the sensitivity, robustness and resilience of the results. The consideration of confidence intervals is also part of the WP.

Results

Results from WP 1 (literature research)

The literature search is based on reviews of relevant institutes and was supplemented by a systematic search of current peer-reviewed literature.

The systematic literature search includes three research strands:

A. Reviews of relevant institutes

B. Umbrella Review

C. Systematic Mapping

The search for reviews from relevant institutes revealed that the WHO and the U.S. Environmental Protection Agency (U.S. EPA) are leaders in providing reviews of air pollutant-related health outcomes. In summary, based on these reports, it can be concluded that the evidence of respiratory health endpoints from short-term ozone exposure is best supported and recommendations, such as WHO guidance or reference values, and estimates for air pollution control measures have been derived.

The search protocol of the search strings B (Umbrella Reviews) and C (Systematic Mapping) has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42019123064 (Zhao et al. 2019) since April 24, 2019, and can be freely accessed there. According to the PRISMA criteria, it is common practice to conduct searches for systematic reviews using at least two literature databases. The databases PubMed and Web of Science (WoS) were selected for this project.

The WHO recommends using Relative Risks to estimate the population attributable fraction (PAF) of pooled evaluations such as meta-analyses (WHO 2020). In addition, meta-analyses can be placed at the highest level of evidence (Biondi-Zoccai 2016). Therefore, this ozone project will focus on meta-analyses of epidemiological studies to evaluate the evidence of exposure endpoint associations. Accordingly, the Umbrella Review was chosen as the review method. An umbrella review is a systematic review of systematic reviews and meta-analyses. Umbrella reviews represent the highest level of evidence synthesis, as the currently available systematic reviews and meta-analyses are combined (Fusar-Poli and Radua 2018). In the current project, meta-analyses of epidemiological studies of all (possibly) ozone-associated health outcomes were researched in the context of the Umbrella Review. In addition to database research (PubMed and WoS), the snowball method was applied. In the course of the Umbrella Review, 70 systematic reviews were identified; 47 of them contained an ozone-related meta-analysis and were evaluated according to the established criteria (from AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews, Shea et al. 2017) and the criteria of the project "Quantification of environmental disease burden due to nitrogen dioxide exposure in Germany" (hereinafter referred to as "NO_2 Project"). The results of the Umbrella Review will not be discussed further in this summary, because all identified systematic reviews refer to short-term exposures, whereas the present project refers to long-term exposures (summer ozone and SOMO35).

Systematic Maps, Mapping Reviews (Grant & Booth 2009) or also Systematic Evidence Maps (SEM) (Wolffe et al. 2019) are the clear presentation of the state of research of a broad field of research (Miake-Lye et al. 2016). "Existing and missing evidence for medical questions are systematically presented in their quantity and with a description of (study) characteristics" (Schmucker et al. 2013, p. 1391). This new type of review (Miake-Lye et al. 2016) differs from classical systematic literature reviews in that the evidence is presented as a whole and does not refer to a limited scope in the systematic review. SEMs are currently widely used internationally (Schmucker et al. 2013). The method of Systematic Mapping was used in the Ozone Project to achieve the following two goals: The first goal of the Systematic Mapping is to assess the biological plausibility of health outcomes that have been evaluated with the strongest evidence based on existing meta-analyses of epidemiological studies. For this purpose, experimental studies (animal studies and mechanistic/in vitro studies) are researched and clearly arranged within the Systematic Mapping. The latest recommendations for systematic reviews require the examination of biological plausibility, which is covered in the current project.

The second goal of systematic mapping was to search for current epidemiological studies since the publication of the last meta-analysis for the corresponding endpoint. These are only original studies and not reviews or meta-analyses that have already been included in the Umbrella Review. The results of the current original studies were used in addition to the qualitative description of the evidence for the endpoint. In addition, effect estimators are to be extracted that may be used to estimate the disease burden.

The assessment of biological plausibility will be performed for the health outcomes with strong evidence. Independent of the evidence review, the health outcomes chronic obstructive pulmonary diseases (COPD) was defined early for the systematic mapping. The reason for this pre-selection is that the currently largest disease burden study includes COPD mortality as the only ozone-related health outcome (GBD 2017 Risk Factor Collaborators 2018). The Global Burden of Disease (GBD) study assessed COPD as a biologically plausible endpoint of ozone. However, this assessment was based solely on epidemiological studies (GBD 2017 Risk Factor Collaborators 2018, Appendix 1, p. 22). The assessment based on experimental studies for COPD and at least one other health outcome was carried out for the first time in this project. After excluding duplicates, the SEM for COPD resulted in 368 hits.

For the disease burden calculations of this project, effect estimates for the ozone outcome pairs were extracted with strong evidence based on epidemiological studies and biological plausibility based on experimental studies.

The selection of effect estimates for the calculation of the disease burden was done as follows: If several effect estimators were published from one study, the effect estimator with the longest observation time was selected (and thus usually the one published last), which corresponds to the usual procedure in meta-analyses of results of systematic reviews. However, additional sensitivity analyses were performed.

As a result of the extensive systematic research of this project, further possible health outcomes resulting from long-term ozone exposures, such as all-cause and cardiovascular mortality and morbidity, as well as metabolic effects such as diabetes, Parkinson's disease and reproductive health indicators, were reviewed. Based on epidemiological studies and biological plausibility, only respiratory mortality and COPD mortality as a subgroup of respiratory mortality were found to be causally associated with long-term exposure to ozone. Other disease entities in connection with long-term ozone exposure were either not sufficiently biologically plausible (cardiovascular diseases, metabolic and neurological diseases) or epidemiologically not sufficiently investigated.

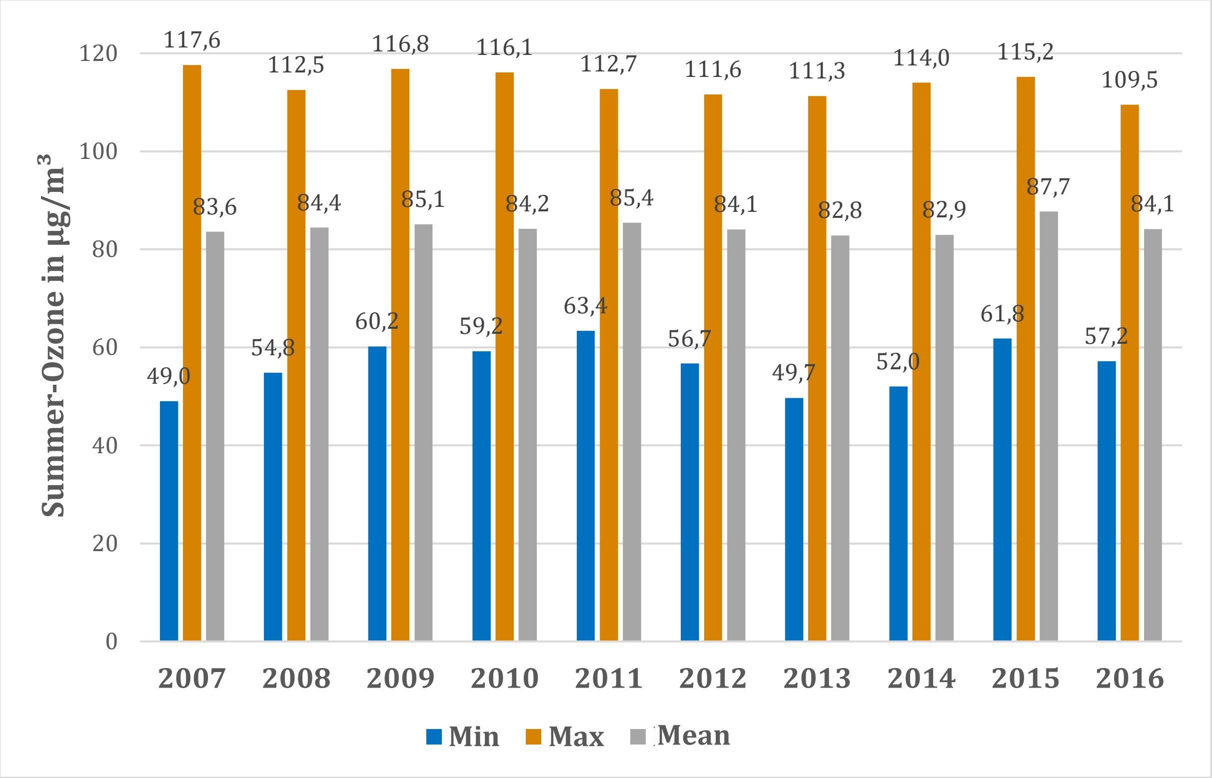
Results from WP 2 and WP 3: Exposure assessment

The basis for the German-wide determination of ozone exposure were area-wide data of the spatial distribution of the ozone background values in the ambient air. The data used for the calculation are those for the years 2007 to 2016, which represent the exposure levels in the rural and urban background at a spatial resolution of about 2 x 2 km^2. The data were generated using the chemical transport model REM/CALGRID (RCG), which was combined with ozone measurement data using the methodology of Optimal Interpolation (OI) (Flemming et al. 2004).

Two exposure estimates were proposed for the project - SOMO35, which is the "annual sum over the daily maxima of the 8-hour moving averages exceeding 35 ppb" (OECD 2008, p. 194) and the mean maximum 8-hour concentration during the summer months, hereinafter referred to as summer-ozone. Since almost all epidemiological studies referred to summer-ozone, the SOMO35 could only be used for disease burden studies to a limited extent.

Figure A 1 shows the distribution of summer ozone for the years 2007 to 2016, with no trend visible over the observation period.

Figure A 1: Mean, minimum, and maximum Summer-Ozone concentrations in Germany for the years 2007 to 2016



Abbreviations: µg/m³, microgram per cubic meter; Max, maximum value; Min, minimum value; mean value summer-ozone: mean value of the daily maxima of the moving 8-hour mean values during the summer months April to September, only data from background stations were used to calculate summer-ozone-area means, maximum and minimum values
Source: Own presentation of data provided by UBA

WP 4 and WP 5: Quantification of the disease burden and uncertainty and scenario analyses

Table A 3 shows the results on respiratory disease burden (ICD-10 code J00-J99) due to long-term exposure to summer ozone in the years 2007 to 2016. As exposure-response function, an estimator summarized by meta-analysis from the studies of Lim et al (2019), Kazemiparkouhi et al (2019), Weichenthal et al (2017), Turner et al (2016), Bentayeb et al (2015) and Lipsett et al (2011) was used; based on the age range of the study populations, the age range was defined as 30 years and older. The results include the attributable fraction, i.e. the proportion of the disease burden that can be attributed to ozone by statistical methods, as well as years of life lost (YLL) in absolute numbers and as a rate (per 100,000 population).

It is important for the interpretation of the shown results that they refer to the German population. Thus, the YLL are not equally distributed among all inhabitants, but rather some inhabitants lose more years of life than others.

Table A 3: Respiratory burden of disease (age> 30 years) due to long-term exposure to summer ozone in Germany in the years 2007 to 2016; lower limit of quantification 65 µg/m³

Year	**2007**	**2008**	**2009**	**2010**	**2011**
Attributable Fraction in % (95 % CI)	4.05 (2.56-5.67)	4.26 (2.69-5.96)	4.50 (2.85-6.29)	4.34 (2.75-6.07)	4.87 (3.09-6.81)
Years of Life Lost (YLL) (95 % CI)	21,822 (13,790-30,540)	23,395 (14,793-32,720)	26,437 (16,728-36,949)	24,768 (16,667-34,627)	27,699 (17,540-38,678)
YLL per 100.000 Inhabitants (95 % CI)	26.53 (16.76-37.12)	28.49 (18.01-39.84)	32.29 (20.43-45.13)	30.29 (19.16-42.35)	34.50 (21.85-48.18)
Year	**2012**	**2013**	**2014**	**2015**	**2016**
Attributable Fraction in % (95 % CI)	4.34 (2.74-6.07)	4.03 (2.55-5.64)	4.10 (2.59-5.74)	5.49 (3.48-7.66)	4.43 (2.80-6.19)
Years of Life Lost (YLL) (95 % CI)	24,169 (15,283-33,803)	24,735 (15,637-34,604)	22,770 (14,393-31,857)	35,481 (22,488-49,497)	27,257 (17,243-38,103)
YLL per 100.000 Inhabitants (95 % CI)	30.05 (19.00-42.03)	30.67 (19.39-42.91)	28.12 (17.77-39.34)	43.44 (27.53-60.59)	33.10 (20.94-46.27)

Abbreviations: CI, confidence interval; **pooled estimate** of the studies Lim et al. 2019, Kazemiparkouhi et al. 2019, Weichenthal et al. 2017, Turner et al. 2016, Bentayeb et al. 2015 and Lipsett et al. 2011: **1.024 (95 % CI: 1.015, 1.034) per 10 µg/m³**

The attributable respiratory disease burden due to summer ozone ranged from 4.03% (CI: 2.55-5.64) (year 2013) to 5.49% (CI: 3.48-7.66) (year 2015). Overall, there is no clear trend in the burden of disease in the period 2007 to 2016 - in the ten year observation period, the burden of disease fluctuated by more than a third from year to year, similar to the trend in ozone concentrations. A comparison of the results with those after adjustment for $PM_{2.5}$ and NO_2 shows slightly lower disease burden after adjustment for other air pollutants.

Table A 4 shows the results for COPD disease burden (ICD-10 code J40-J44) due to long-term exposure to summer ozone in the years 2007 to 2016. The attributable fraction ranges from 6.11 % (year 2013) to 8.29 % (year 2015), the lost years of life per 100,000 inhabitants in the range of 18.33 YLL (confidence interval, CI: 14.02-22.08) (year 2007) to 35.77 YLL (CI: 27.45-42.98) (year 2015). Similar to the respiratory disease burden, there is no clear trend in the disease burden over the observation period.

Table A 4: COPD- burden of disease (age> 30 years) due to long-term exposure to summer ozone in Germany in the years 2007 to 2016; lower limit of quantification 65 µg/m³

Year	2007	2008	2009	2010	2011
Attributable Fraction in % (95 % CI)	6.15 (4.70-7.40)	6.46 (4.94-7.78)	6.81 (5.22-8.20)	6.58 (5.04-7.92)	7.37 (5.65-8.87)
Years of Life Lost (YLL) (95 % CI)	15,078 (11,535-18,162)	16,097 (12,323-19,380)	19,076 (14,612-22,953)	18,763 (14,369-22,583)	21,243 (16,285-25,543)
YLL per 100.000 Inhabitants (95 % CI)	18.33 (14.02-22.08)	19.60 (15.01-23.60)	23.30 (17.85-28.03)	22.95 (17.57-27.62)	26.46 (20.29-31.82)
Year	**2012**	**2013**	**2014**	**2015**	**2016**
Attributable Fraction in % (95 % CI)	6.58 (5.04-7.92)	6.11 (4.68-7.36)	6.23 (4.76-7.50)	8.29 (6.36-9.96)	6.71 (5.14-8.07)
Years of Life Lost (YLL) (95 % CI)	19,006 (14,549-22,881)	19,751 (15,116-23,784)	18,828 (14,408-22,673)	29,222 (22,421-35,111)	22,993 (17,609-27,672)
YLL per 100.000 Inhabitants (95 % CI)	23.63 (18.09-28.45)	24.49 (18.74-29.49)	23.25 (17.79-28.00)	35.77 (27.45-42.98)	27.92 (21.38-33.60)

Abbreviations: CI, confidence interval; **pooled estimate** of the studies Lim et al. 2019, Kazemiparkouhi et al. 2019, and Turner et al. 2016: **1,037 (95 % KI: 1,028, 1,045) pro 10 µg/m³**

Additionally, an estimation of the disease burden of summer ozone was performed based on effect estimates adjusted for particulate matter and NO_2. While the respiratory burden of disease decreased slightly after adjustment for particulate matter and NO_2 when using EWF, the burden of disease for COPD is even higher.

With regard to the second ozone exposure indicator, SOMO35, only the respiratory disease burden could be calculated on the basis of a single, but somewhat older risk estimator from 2009 (Jerrett et al. 2009). A comparison with the current disease burden estimates for summer ozone is therefore only of limited value.

In scenario analyses, a limit of 71 µg/m^3 for respiratory and COPD disease burden was considered in addition to 65 µg/m^3 as lower limit of quantification. Even when using the more conservative lower limit of 71 µg/m^3, summer ozone-related YLLs per 100,000 inhabitants still showed a range of 17.72 (95% confidence interval, CI: 11.16-24.88) to 32.72 (95% CI: 20.68-45.78) for the respiratory disease burden. For COPD disease burden, YLLs per 100,000 population ranged from 12.29 (95% CI: 9.38-14.85) to 27.06 (95% CI: 20.70-32.59). The width of the confidence intervals is mainly determined by the fact that, depending on the choice of the lower limit of quantification, no health risk from summer ozone is assumed for a varying part of the population and thus no variation of the effect – in the form of the CI of the EWF. For example, with a lower limit of quantification of 65 µg/m^3 no health risk is assumed for about 0.01 % (year 2015) to 1.10 % (year 2007) of the German population – with a lower limit of quantification of 71 µg/m^3 this is the case for about 0.03 % (year 2015) to 4.49 % (year 2007) of the population.

In addition to the year-to-year variations in the burden of disease from ozone resulting from changes in ozone concentrations, the underlying risk estimators play a crucial role in quantifying uncertainties. In addition, there is the qualitative assessment of the uncertainties due to the question of the transferability of the risks, which originate mainly from North American studies, to the situation in Germany, which cannot be answered conclusively. Other factors of uncertainty such as the errors in extrapolating the population of Germany according to the census and the generic uncertainties in the cause of death statistics are considered less significant.

Discussion and Conclusions

The studies, which quantified the burden of disease caused by long-term exposure to ozone are based on the method developed by the WHO for estimating the burden of disease caused by environmental factors (Prüss-Üstün et al. 2003). However, these studies differ significantly in the input data. Almost all studies refer to the effect estimator published by Jerrett et al. in 2009. Since the groundbreaking publication of Jerrett et al. (2009), several other long-term studies have been published, which, in the context of this project, for the first time could be used as the basis for a disease burden calculation. Due to the different input data used, a comparison of the disease burden estimates between the different studies is only meaningful if the uncertainties are strictly observed.

In October 2020, the last disease burden estimate from long-term ozone exposure was published exclusively on COPD mortality as a result of the GBD study (GBD 2019 Risk Factors Collaborators). These estimates were based on the risk estimator of 1.06 (95 % CI: 1.02-1.10) for a 10 ppb increase in summer ozone averaged over three cohorts (meta-analysis with inverse variance). For the year 2016, 43.05 ozone-related YLLs per 100 000 persons (95 % CI: 18.14-74.06) were published for Germany. These figures are slightly above the YLLs estimated in the present project - 18.33 YLL (95 % CI: 14.02-22.08) in 2007 to 35.77 YLL (95 % CI: 27.45-42.98) in 2015). The following factors may explain the deviation: The GBD study assumes slightly higher ozone exposure than estimated in the current study. The GBD study estimate is based on a grid of 11 x 11 km, whereas in the current study a high resolution of 2 x 2 km could be used.

Furthermore, the standardized life expectancy used in the GBD study is higher than the life expectancy documented in Germany. Furthermore, the GBD study estimated the disease burden for all age groups from 25 years of age, whereas the current study has set the lower age limit at 30 years. Negligible factors that may not have influenced the deviation or may have influenced it to a very small extent are slight variations in the level of risk estimates used as well as slight variations in the ICD-10 codes used and lower quantification limits.

The first estimates for the respiratory disease burden of ozone are interesting, since effect estimates are adjusted for other air pollutants such as $PM_{2.5}$ and NO_2, and for temperature. Although the estimates were slightly lower, these results indicate that ozone affects the respiratory burden of disease independent of other air pollutants. However, it should be noted that the level of ozone concentrations and the pollutant mix in the USA (almost all studies considered were conducted there) are not necessarily comparable to those in Germany, among other things because of a different emitter structure, different climatic conditions and thus atmospheric transformation processes. Furthermore, it needs to be interpreted and discussed why the respiratory disease burden due to ozone is (slightly) lower compared to the COPD disease burden. This result does not seem plausible at first glance because COPD mortality is a subgroup of respiratory mortality. However, the calculations of the respiratory and COPD disease burden are based on different risk estimates. The risk estimator used for the COPD disease burden is higher than the one used for the respiratory disease burden and therefore leads to a higher disease burden for COPD. In addition, the adverse health effects of ozone can be specifically demonstrated for COPD, and the effects on the respiratory disease burden are mainly caused by COPD. Respiratory mortality is mainly composed of COPD mortality and mortality due to pneumonia. Since the latter is less strongly associated with ozone effects, the health effects of ozone are attenuated. Finally, it should be noted that disease burdens from different models cannot simply be added or subtracted. In this respect, the results presented are plausible on closer examination.

The European Environmental Agency (EEA 2019) has determined the ozone-related YLLs and attributable deaths for Germany using SOMO35. The result was 24,400 YLL (30 YLL per 100,000 inhabitants). Again, a comparison with the results of this project can only be made with caution, because different health outcomes and different exposures were used as a basis (EEA: all-cause mortality and short-term effects, present study: respiratory mortality and long-term effects). In the present study, 7,604 YLL (9.23 YLL per 100,000 population was determined. A comparison with the results of the VeGAS project (Hornberg et al. 2013) is not made because of the even more clearly different input data (short-term effect risks). It should also be noted that the combination of population-weighted long-term exposures with effect estimates from short-term exposure studies raises methodological questions.

Given the complexity of the models used here and the uncertainties of the input data, a presentation of the strengths and weaknesses of this project is absolutely necessary.

This project has several undisputed strengths. These include:

- The quantification of the burden of disease caused by ozone is based on the concept of the environmental burden of disease developed by the WHO (Prüss-Üstün et al. 2003) We consider the application of this model a strength because it has become the relevant standard and reduces the already existing heterogeneity between different disease burden studies. Nevertheless, it is worth recalling the discussion of the limitations of this approach as discussed in Hornberg et al (2013) and Srebotnjak et al (2015).

- The Systematic Umbrella Review and especially the three Systematic Mappings represent a modern concept to assess numerous study results including experimental studies concerning the evidence for an underlying causality.
- The use of the most recent effect estimators of the American Cancer Society (ACS, Turner et al. 2016) and the Canadian Census Health and Environment Cohort (CanCHEC, Weichenthal et al. 2017) as well as other effect estimators published for the first time is considered an additional strength of this study.
- The quantitative summary of effect estimates from different studies (meta-analyses including the confidence intervals of the individual studies) is also a strength of this project because almost all previous disease burden studies on ozone refer to only one effect estimator (von Jerrett et al. 2009), which has been critically noted in the literature (Prueitt & Goodman 2011).
- Effect estimates adjusted for particulate matter, NO_2, and temperature were used to estimate the disease burden of ozone. This is particularly important because for years the use of estimators from "single-pollutant" models has been criticized, often without remedy.
- We consider the title given by the client on the disease burden caused by ozone and the focus on causal effects derived from it as a strength of the project because this focus makes a discussion of causality in association studies unnecessary.
- The resolution of the area-related ozone concentration for a grid of 2 km x 2 km in this study is higher than in all other comparable studies.
- Furthermore, we consider the numerous sensitivity analyses including or excluding individual studies on effect estimators as well as the two exposure indicators on summer-ozone and SOMO35 as strengths because they allowed us to assess the consistency and robustness of the results.

However, this project also has a number of limitations, which will be briefly described below.

- The measures estimated for the burden of disease caused by environmental factors represent key figures for public health. The results of studies on the Environmental Burden of Disease (EBD) are therefore to be used exclusively to derive statements at the population level. Information on the health status of individual individuals cannot be derived from EBD studies. Furthermore, these are estimates that are determined by model calculations. Such model calculations require different assumptions to be made, such as the exposure-response function used or the remaining life expectancy at death.
- In general, the uncertainties of the results of a disease burden study cannot be smaller than the uncertainties of the input data. In this respect, the uncertainties of the input data must be stated.
- The effect estimates originate mainly from large North American studies and the transferability to German conditions is a necessary pragmatic approach because no relevant data from Germany or Europe are available. Of course, this involves some uncertainties.

- With regard to the calculated exposure to ozone, it must be clearly pointed out that this is only the modelled ozone concentration in a certain (small-scale) grid over Germany. This is a very simplified (though common) procedure to estimate exposure, especially because of the different residence times of persons.
- The uncertainty ranges of the disease burden estimates by ozone, as, for example, shown by the confidence intervals, are very large. For this reason, an explicit warning should be issued against uncritical use of the point estimate without specifying the confidence interval.
- Due to the clear methodological differences in the calculation of the burden of disease caused by the air pollutants particulate matter, NO_2, and ozone in Germany, a direct comparison is only possible to a limited extent.
- The ozone concentrations averaged over the summer months and also the SOMO35 cannot adequately represent possible effects of peak exposures.
- When interpreting the results on YLL, it should be taken into account that the lost life years are not equally distributed across all age groups.
- Despite the inherent uncertainties and limitations, we consider the results of this project to be robust overall, provided that the summaries and brief reports are not limited to the point estimates and that the confidence intervals are always stated as a measure of uncertainty.

In summary, the following can be concluded from the present project:

a. Long-term exposure to ozone also contributes to the burden of disease in the German general population. Given a possible increase in ozone concentration (due to climate change), more intensive research on the health effects of ozone is necessary.

b. Estimates of the burden of disease caused by ozone vary greatly from year to year due to variations in ozone concentrations from year to year. It is not recommended to calculate the burden of disease for only one arbitrarily selected year.

c. Even an observation period of ten years is too short to quantify trends in ozone concentrations and thus in the burden of disease.

d. For Europe, and especially for Germany, there is a lack of reliable epidemiological data on the long-term effects of ozone, which should be compensated by secondary data analyses in the context of already implemented projects and by new cohort studies.

e. Interactions of long-term ozone exposure with volatile organic compounds, ultrafine particles and green spaces have not yet been researched internationally with regard to health effects. This is a challenging and innovative field of research.

f. There is a lack of reliable epidemiological results on long-term ozone exposure and the occurrence of asthma and hay fever.

Danksagung

Ein herzliches Dankeschön an die Kolleginnen und Kollegen, die das Vorhaben im Rahmen des Expertinnen- und Expertenworkshops kritisch diskutiert und Anregungen für die fachliche Diskussion gegeben haben: Dr. J. Cyrys, Prof. Dr. C. Hornberg, Dr. O. Mekel, Dr. H. Niemann, Dr. T. Schikowski, Dr. E. von der Lippe. Des Weiteren bedanken wir uns bei den MitarbeiterInnen und den FachbegleiterInnen des Umweltbundesamtes: U. Dauert, S. Feigenspan, A. Krug, S. Kienzler, Dr. HG Mücke, Dr. S. Nordmann, Dr. D. Plaß, Dr. W. Straff, M.Tobollik, D. Wintermeyer

Die Autorinnen und Autoren erklären, dass keine Interessenskonflikte vorliegen.

6 Quellenverzeichnis

Ab Manan, N., Noor Aizuddin, A., Hod, R. (2018): Effect of Air Pollution and Hospital Admission: A Systematic Review. In: Ann Glob Health, 2018, 84, 4, S. 670-678

Alam, S., Lang, J.J., Drucker, A.M., Gotay, C., Kozloff, N., Mate, K., Patten, S.B., Orpana, H.M., Afshin, A., Cahill, L.E. (2019): Assessment of the burden of diseases and injuries attributable to risk factors in Canada from 1990 to 2016: an analysis of the Global Burden of Disease Study. In: CMAJ Open, 2019, 7, S. E140-e148

An, R., Ji, M., Yan, H., Guan, C. (2018): Impact of ambient air pollution on obesity: a systematic review. In: Int J Obes (Lond), 2018, 42, S. 1112-1126

Anderson, H.R., Atkinson, R.W., Peacock, J.L., Marston, L., Konstantinou, K. (2004): Meta-analysis of time-series studies and panel studies of particulate matter (PM) and Ozone (O3). World Health Organization (WHO), Copenhagen, https://apps.who.int/iris/handle/10665/107557

Anenberg, S.C., Horowitz, L.W., Tong, D.Q., West, J.J. (2010): An estimate of the global burden of anthropogenic ozone and fine particulate matter on premature human mortality using atmospheric modeling. In: Environ Health Perspect, 2010, 118, S. 1189-1195

Atkinson, R.W., Butland, B.K., Dimitroulopoulou, C., Heal, M.R., Stedman, J.R., Carslaw, N., Jarvis, D., Heaviside, C., Vardoulakis, S., Walton, H., Anderson, H.R. (2016): Long-term exposure to ambient ozone and mortality: a quantitative systematic review and meta-analysis of evidence from cohort studies. In: BMJ open, 2016, 2, S. e009493

Atkinson, R.W., Cohen, A., Mehta, S., Anderson, H.R. (2012): Systematic review and meta-analysis of epidemiological time-series studies on outdoor air pollution and health in Asia. In: Air Qual Atmos Health, 2012, 5, S. 383-391

Avdalovic, M.V., Tyler, N.K., Putney, L., Nishio, S.J., Quesenberry, S., Singh, P.J., Miller, L.A., Schelegle, E.S., Plopper, C.G., Vu, T., Hyde, D.M. (2012): Ozone exposure during the early postnatal period alters the timing and pattern of alveolar growth and development in nonhuman primates. In: Anat Rec (Hoboken), 2012, 295, S. 1707-1716

Bass, V., Gordon, C.J., Jarema, K.A., MacPhail, R.C., Cascio, W.E., Phillips, P.M., Ledbetter, A.D., Schladweiler, M.C., Andrews, D., Miller, D., Doerfler, D.L., Kodavanti, U.P. (2013): Ozone induces glucose intolerance and systemic metabolic effects in young and aged brown Norway rats. In: Toxicol Appl Pharmacol, 2013, 273, S. 551-560

Bates, S., Clapton, J., Coren, E. (2007): Systematic maps to support the evidence base in social care. In: The Policy Press, 2007, 3, S. 539-551

Bazyar, J., Pourvakhshoori, N., Khankeh, H., Farrokhi, M., Delshad, V., Rajabi, E. (2019): A comprehensive evaluation of the association between ambient air pollution and adverse health outcomes of major organ systems: a systematic review with a worldwide approach. In: Environ Sci Pollut Res Int, 2019, 26, S. 12648-12661

Belbasis, L., Bellou, V., Evangelou, E., Ioannidis, J.P., Tzoulaki, I. (2015): Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. In: Lancet Neurol, 2015, 14, S. 263-273

Bell, M.L., Dominici, F., Samet, J.M. (2005): A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. In: Epidemiology, 2005, 16, S. 436-445

Bellou, V., Belbasis, L., Tzoulaki, I., Evangelou, E., Ioannidis, J.P. (2016): Environmental risk factors and Parkinson's disease: An umbrella review of meta-analyses. In: Parkinsonism Relat Disord, 2016, 23, S. 1-9

Bellou, V., Belbasis, L., Tzoulaki, I., Middleton, L.T., Ioannidis, J.P.A., Evangelou, E. (2017): Systematic evaluation of the associations between environmental risk factors and dementia: An umbrella review of systematic reviews and meta-analyses. In: Alzheimers Dement, 2017, 13, S. 406-418

Bentayeb, M., Wagner, V., Stempfelet, M., Zins, M., Goldberg, M., Pascal, M., Larrieu, S., Beaudeau, P., Cassadou, S., Eilstein, D., Filleul, L., Le Tertre, A., Medina, S., Pascal, L., Prouvost, H., Quénel, P., Zeghnoun, A., Lefranc, A. (2015): Association between long-term exposure to air pollution and mortality in France: A 25-year follow-up study. In: Environ Int, 2015, 85, S. 5-14

Biller, H., Holz, O., Windt, H., Koch, W., Muller, M., Jorres, R.A., Krug, N., Hohlfeld, J.M. (2011): Breath profiles by electronic nose correlate with systemic markers but not ozone response. In: Respir Med, 2011, 105, S. 1352-1363

Biondi-Zoccai, G. (2016): Umbrella reviews: Evidence Synthesis with Overviews of Reviews and Meta-Epidemiologic Studies. 1. Auflage, Springer International, Cham

Bonzini, M., Carugno, M., Grillo, P., Mensi, C., Bertazzi, P.A., Pesatori, A.C. (2010): Impact of ambient air pollution on birth outcomes: systematic review of the current evidences. In: Med Lav, 2010, 101, S. 341-363

Buringh, E., Opperhuizen, A., Aben, J., Ameling, C.B., Beck, J., Boere, A.J.F., Breugel, P.B.v., Brink, H.M.t., Brink, R.M.M.v.d., Buijsman, E., Brunekreef, B., Buringh, E., Cassee, F.R., Dekkers, A.L.M., Dolmans, J., Eerens, H.C., Fischer, P.H., Harmelen, A.K.v., Keuken, M.P., Kooter, I.M., Loon, M.v., Loveren, H.v., Mara, M., Matthijsen, J., Noordijk, H., Opperhuizen, A., Schaap, M., Schlesinger, R.B., Slanina, J., Smeets, P., Smeets, W.L.M., Spoelstra, H., Steerenberg, P.A., Visschedijk, A.J.H., Visser, H., Vries, W.J.d., Weijers, E., Winter, R.d. (2002): On health risks of ambient PM in the Netherlands. Full report: Netherlands Aerosol Programme. National Institute for Public Health and the Environment, Bilthoven, https://www.rivm.nl/bibliotheek/rapporten/650010032.pdf

Buteau, S., Goldberg, M.S. (2016): A structured review of panel studies used to investigate associations between ambient air pollution and heart rate variability. In: Environ Res, 2016, 148, S. 207-247

Cai, Y., Zhang, B., Ke, W., Feng, B., Lin, H., Xiao, J., Zeng, W., Li, X., Tao, J., Yang, Z., Ma, W., Liu, T. (2016): Associations of Short-Term and Long-Term Exposure to Ambient Air Pollutants With Hypertension: A Systematic Review and Meta-Analysis. In: Hypertension, 2016, 68, S. 62-70

Canese, K., Weis, S. (2013): PubMed: The Bibliographic Database. In: Beck, J., Benson, D., Coleman, J., Hoeppner, M., Johnson, M., Maglott, D., Mizrachi, I., Morris, R., Ostell, J., Pruitt, K., Rubinstein, W., Sayers, E., Sirotkin, K., Tatusova, T. (Hrsg.): The NCBI Handbook [Internet] 2nd edition. Bethesda, National Center for Biotechnology Information (US)

Carre, J., Gatimel, N., Moreau, J., Parinaud, J., Leandri, R. (2017): Does air pollution play a role in infertility?: a systematic review. In: Environ Health, 2017, 16, S. 82

Chen, E.K., Zmirou-Navier, D., Padilla, C., Deguen, S. (2014): Effects of air pollution on the risk of congenital anomalies: a systematic review and meta-analysis. In: Int J Environ Res Public Health, 2014, 11, S. 7642-7668

Clapton, Janet, Rutter, D., Sharif, N. (2009): SCIE Systematic mapping guidance. Social Care Institute for Excellence (SCIE), London, https://www.scie.org.uk/publications/researchresources/rr03.pdf

Clarivate Analytics. (2018): Web of Science. Trust the difference. Clarivate Analytics, Boston, http://wokinfo.com/

Clarivate Analytics. (2019): Web of Science platform: Web of Science: Summary of Coverage. Clarivate Analytics, Boston, https://clarivate.libguides.com/webofscienceplatform/coverage

Cohen, A.J., Brauer, M., Burnett, R., Anderson, H.R., Frostad, J., Estep, K., Balakrishnan, K., Brunekreef, B., Dandona, L., Dandona, R., Feigin, V., Freedman, G., Hubbell, B., Jobling, A., Kan, H., Knibbs, L., Liu, Y., Martin, R., Morawska, L., Pope, C.A., Shin, H., Straif, K., Shaddick, G., Thomas, M., van Dingenen, R., van Donkelaar, A., Vos, T., Murray, C.J.L., Forouzanfar, M.H. (2017): Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. In: Lancet (Lond), 2017, 389, S. 1907-1918

Conforti, A., Mascia, M., Cioffi, G., De Angelis, C., Coppola, G., De Rosa, P., Pivonello, R., Alviggi, C., De Placido, G. (2018): Air pollution and female fertility: a systematic review of literature. In: Reprod Biol Endocrinol, 2018, 16, S. 117

Crouse, D.L., Peters, P.A., Hystad, P., Brook, J.R., van Donkelaar, A., Martin, R.V., Villeneuve, P.J., Jerrett, M., Goldberg, M.S., Pope, C.A., 3rd, Brauer, M., Brook, R.D., Robichaud, A., Menard, R., Burnett, R.T. (2015): Ambient PM2.5, O_3, and NO_2 Exposures and Associations with Mortality over 16 Years of Follow-Up in the Canadian Census Health and Environment Cohort (CanCHEC). In: Environ Health Perspect, 2015, 123, S. 1180-1186

Damera, G., Jester, W.F., Jiang, M., Zhao, H., Fogle, H.W., Mittelman, M., Haczku, A., Murphy, E., Parikh, I., Panettieri, R.A., Jr. (2010): Inhibition of myristoylated alanine-rich C kinase substrate (MARCKS) protein inhibits ozone-induced airway neutrophilia and inflammation. In: Exp Lung Res, 2010, 36, S. 75-84

Damera, G., Zhao, H.J., Wang, M., Smith, M., Kirby, C., Jester, W.F., Lawson, J.A., Panettieri, R.A. (2009): Ozone modulates IL-6 secretion in human airway epithelial and smooth muscle cells. In: Am J Physiol-Lung Cell Mol Physiol, 2009, 296, S. L674-L683

Danesh Yazdi, M., Wang, Y., Di, Q., Zanobetti, A., Schwartz, J. (2019): Long-term exposure to PM2.5 and ozone and hospital admissions of Medicare participants in the Southeast USA. In: Environ Int, 2019, 130, S. 104879

de Hollander, A.E., Melse, J.M., Lebret, E., Kramers, P.G. (1999): An aggregate public health indicator to represent the impact of multiple environmental exposures. In: Epidemiology, 1999, 10, S. 606-617

de Hollander, A.E.M., Melse, J.M. (2004): Assessing and evaluating the health impact of environmental exposures. “Deaths, DALYs or Dollars?” Universiteit Utrecht, Utrecht, https://dspace.library.uu.nl/bitstream/handle/1874/315/full.pdf

Deng, Z., Gao, Z.C., Ge, H.Q., Zhang, L.R., Zhou, J.J., Zhu, Z.P., Wu, D.Y., Sun, S.Y., Chen, L., Pu, X.P. (2013): Treatment responses of procaterol and CD38 inhibitors in an ozone-induced airway hyperresponsiveness mice model. In: Biol Pharm Bul, 2013, 36, S. 1348-1355

DeStatis (2016): Todesursachenstatistik: Todesursachen in Deutschland. Statistisches Bundesamt (DeStatis), Wiesbaden https://www.destatis.de/DE/Methoden/Qualitaet/Qualitaetsberichte/Gesundheit/todesursachen.pdf?__blob=publicationFile

DWD (2019): Climatological maps of Germany. Deutscher Wetterdienst (DWD), Offenbach, https://www.dwd.de/EN/ourservices/klimakartendeutschland/klimakartendeutschland.html;jsessionid=9839AFA440C6A0329670A999A971C9EA.live21071?nn=519080

Dye, J.A., Gibbs-Flournoy, E.A., Richards, J.H., Norwood, J., Kraft, K., Hatch, G.E. (2017): Neonatal rat age, sex and strain modify acute antioxidant response to ozone. In: Inhal Toxicol, 2017, 29, S. 291-303

Dzhambov, A.M., Dimitrova, D.D., Turnovska, T.H. (2016): Long-Term Residential Ambient Air Pollution and Rheumatoid Arthritis: A Systematic Review. In: Health Scope, 2016, 5, S. 9

EC (2019): Air Quality Standards 2019. European Commission (EC), Brussels, https://ec.europa.eu/environment/air/quality/standards.htm

EEA (2009): Assessment of ground-level ozone in EEA member countries, with a focus on long-term trends. European Environment Agency (EEA), Copenhagen, http://www.eea.europa.eu/publications/assessment-of-ground-level-ozone-in-eeamember-countries-with-a-focus-on-long-term-trends?utm_source=EEASubscriptions&utm_medium=RSSFeeds&utm_campaign=Generic

EEA (2019): Assessing the risks to health from air pollution. European Environment Agency (EEA), Copenhagen, https://www.eea.europa.eu/themes/air/health-impacts-of-air-pollution/assessing-the-risks-to-health

Egger, M., Davey Smith, G., Schneider, M., Minder, C. (1997): Bias in meta-analysis detected by a simple, graphical test. In: Bmj, 1997, 315, S. 629-634

Elshahidi, M.H. (2019): Outdoor Air Pollution and Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis. In: Iran J Public Health, 2019, 48, S. 9-19

Faridi, S., Shamsipour, M., Krzyzanowski, M., Kunzli, N., Amini, H., Azimi, F., Malkawi, M., Momeniha, F., Gholampour, A., Hassanvand, M.S., Naddafi, K. (2018): Long-term trends and health impact of PM2.5 and O3 in Tehran, Iran, 2006-2015. In: Environ Int, 2018, 114, S. 37-49

Fei, X., Bao, W., Zhang, P., Zhang, X., Zhang, G., Zhang, Y., Zhou, X., Zhang, M. (2017): Inhalation of progesterone inhibits chronic airway inflammation of mice exposed to ozone. In: Mol Immunol, 2017, 85, S. 174-184

Flemming, J., van Loon, M., Stern, R. (2004): Data Assimilation for Ctm Based on Optimum Interpolation and Kalman Filter. In: Borrego C., Incecik S. (Hrsg.): Air Pollution Modeling and Its Application XVI. Springer, Boston, S. 372-382

Flores-Pajot, M.C., Ofner, M., Do, M.T., Lavigne, E., Villeneuve, P.J. (2016): Childhood autism spectrum disorders and exposure to nitrogen dioxide, and particulate matter air pollution: A review and meta-analysis. In: Environ Res, 2016, 151, S. 763-776

Forouzanfar, M.H., Alexander, L., Anderson, H.R., Bachman, V.F., Biryukov, S., Brauer, M., Burnett, R., Casey, D., Coates, M.M., Cohen, A., Delwiche, K., Estep, K., Frostad, J.J., Astha, K.C., Kyu, H.H., Moradi-Lakeh, M., Ng, M., Slepak, E.L., Thomas, B.A., Wagner, J., Aasvang, G.M., Abbafati, C., Abbasoglu Ozgoren, A., Abd-Allah, F., Abera, S.F., Aboyans, V., Abraham, B., Abraham, J.P., Abubakar, I., Abu-Rmeileh, N.M., Aburto, T.C., Achoki, T., Adelekan, A., Adofo, K., Adou, A.K., Adsuar, J.C., Afshin, A., Agardh, E.E., Al Khabouri, M.J., Al Lami, F.H., Alam, S.S., Alasfoor, D., Albittar, M.I., Alegretti, M.A., Aleman, A.V., Alemu, Z.A., Alfonso-Cristancho, R., Alhabib, S., Ali, R., Ali, M.K., Alla, F., Allebeck, P., Allen, P.J., Alsharif, U., Alvarez, E., Alvis-Guzman, N., Amankwaa, A.A., Amare, A.T., Ameh, E.A., Ameli, O., Amini, H., Ammar, W., Anderson, B.O., Antonio, C.A., Anwari, P., Argeseanu Cunningham, S., Arnlov, J., Arsenijevic, V.S., Artaman, A., Asghar, R.J., Assadi, R., Atkins, L.S., Atkinson, C., Avila, M.A., Awuah, B., Badawi, A., Bahit, M.C., Bakfalouni, T., Balakrishnan, K., Balalla, S., Balu, R.K., Banerjee, A., Barber, R.M., Barker-Collo, S.L., Barquera, S., Barregard, L., Barrero, L.H., Barrientos-Gutierrez, T., Basto-Abreu, A.C., Basu, A., Basu, S., Basulaiman, M.O., Batis Ruvalcaba, C., Beardsley, J., Bedi, N., Bekele, T., Bell, M.L., Benjet, C., Bennett, D.A., Benzian, H., Bernabe, E., Beyene, T.J., Bhala, N., Bhalla, A., Bhutta, Z.A., Bikbov, B., Bin Abdulhak, A.A., Blore, J.D., Blyth, F.M., Bohensky, M.A., Bora Basara, B., Borges, G., Bornstein, N.M., Bose, D., Boufous, S., Bourne, R.R., Brainin, M., Brazinova, A., Breitborde, N.J., Brenner, H., Briggs, A.D., Broday, D.M., Brooks, P.M., Bruce, N.G., Brugha, T.S., Brunekreef, B., Buchbinder, R., Bui, L.N., Bukhman, G., Bulloch, A.G., Burch, M., Burney, P.G., Campos-Nonato, I.R., Campuzano, J.C., Cantoral, A.J., Caravanos, J., Cardenas, R., Cardis, E., Carpenter, D.O., Caso, V., Castaneda-Orjuela, C.A., Castro, R.E., Catala-Lopez, F., Cavalleri, F., Cavlin, A., Chadha, V.K., Chang, J.C., Charlson, F.J., Chen, H., Chen, W., Chen, Z., Chiang, P.P., Chimed-Ochir, O., Chowdhury, R., Christophi, C.A., Chuang, T.W., Chugh, S.S., Cirillo, M., Classen, T.K., Colistro, V., Colomar, M., Colquhoun, S.M., Contreras, A.G., Cooper, C., Cooperrider, K., Cooper, L.T., Coresh, J., Courville, K.J., Criqui, M.H., Cuevas-Nasu, L., Damsere-Derry, J., Danawi, H., Dandona, L., Dandona, R., Dargan, P.I., Davis, A., Davitoiu, D.V., Dayama, A., de Castro, E.F., De la Cruz-Gongora, V., De Leo, D., de Lima, G., Degenhardt, L., del Pozo-Cruz, B., Dellavalle, R.P., Deribe, K., Derrett, S., Des Jarlais, D.C., Dessalegn, M., deVeber, G.A., Devries, K.M., Dharmaratne, S.D., Dherani, M.K., Dicker, D., Ding, E.L., Dokova, K., Dorsey, E.R., Driscoll, T.R., Duan, L., Durrani, A.M., Ebel, B.E., Ellenbogen, R.G., Elshrek, Y.M., Endres, M., Ermakov, S.P., Erskine, H.E., Eshrati, B., Esteghamati, A., Fahimi, S., Faraon, E.J., Farzadfar, F., Fay, D.F., Feigin, V.L., Feigl, A.B., Fereshtehnejad, S.M., Ferrari, A.J., Ferri, C.P., Flaxman, A.D., Fleming, T.D., Foigt, N., Foreman, K.J., Paleo, U.F., Franklin, R.C., Gabbe, B., Gaffikin, L., Gakidou, E., Gamkrelidze, A., Gankpe, F.G., Gansevoort, R.T., Garcia-Guerra, F.A., Gasana, E., Geleijnse, J.M., Gessner, B.D., Gething, P., Gibney, K.B., Gillum, R.F., Ginawi, I.A., Giroud, M., Giussani, G., Goenka, S., Goginashvili, K., Gomez Dantes, H., Gona, P., Gonzalez de Cosio, T., Gonzalez-Castell, D., Gotay, C.C., Goto, A., Gouda, H.N., Guerrant, R.L., Gugnani, H.C., Guillemin, F., Gunnell, D., Gupta, R., Gupta, R., Gutierrez, R.A., Hafezi-Nejad, N., Hagan, H., Hagstromer, M., Halasa, Y.A., Hamadeh, R.R., Hammami, M., Hankey, G.J., Hao, Y., Harb, H.L., Haregu, T.N., Haro, J.M., Havmoeller, R., Hay, S.I., Hedayati, M.T., Heredia-Pi, I.B., Hernandez, L., Heuton, K.R., Heydarpour, P., Hijar, M., Hoek, H.W., Hoffman, H.J., Hornberger, J.C., Hosgood, H.D., Hoy, D.G., Hsairi, M., Hu, G., Hu, H., Huang, C., Huang, J.J., Hubbell, B.J., Huiart, L., Husseini, A., Iannarone, M.L., Iburg, K.M., Idrisov, B.T., Ikeda, N., Innos, K., Inoue, M., Islami, F., Ismayilova, S., Jacobsen, K.H., Jansen, H.A., Jarvis, D.L., Jassal, S.K., Jauregui, A., Jayaraman, S., Jeemon, P., Jensen, P.N., Jha, V., Jiang, F., Jiang, G., Jiang, Y., Jonas, J.B., Juel, K., Kan, H., Kany Roseline, S.S., Karam, N.E., Karch, A., Karema, C.K., Karthikeyan, G., Kaul, A., Kawakami, N., Kazi, D.S., Kemp, A.H., Kengne, A.P., Keren, A., Khader, Y.S., Khalifa, S.E., Khan, E.A., Khang, Y.H., Khatibzadeh, S., Khonelidze, I., Kieling, C., Kim, D., Kim, S., Kim, Y., Kimokoti, R.W., Kinfu, Y., Kinge, J.M., Kissela, B.M., Kivipelto, M., Knibbs, L.D., Knudsen, A.K., Kokubo, Y., Kose, M.R., Kosen, S., Kraemer, A., Kravchenko, M., Krishnaswami, S., Kromhout, H., Ku, T., Kuate Defo, B., Kucuk Bicer, B., Kuipers, E.J., Kulkarni, C., Kulkarni, V.S., Kumar, G.A., Kwan, G.F., Lai, T., Lakshmana Balaji, A., Lalloo, R., Lallukka, T., Lam, H., Lan, Q., Lansingh, V.C., Larson, H.J., Larsson, A., Laryea, D.O., Lavados, P.M., Lawrynowicz, A.E., Leasher, J.L., Lee, J.T., Leigh, J., Leung, R., Levi, M., Li, Y., Li, Y., Liang, J., Liang, X., Lim, S.S., Lindsay, M.P., Lipshultz, S.E., Liu, S., Liu, Y., Lloyd, B.K., Logroscino, G., London, S.J., Lopez, N., Lortet-Tieulent, J., Lotufo, P.A., Lozano, R., Lunevicius, R., Ma, J., Ma, S., Machado, V.M., MacIntyre, M.F., Magis-Rodriguez, C., Mahdi, A.A., Majdan, M., Malekzadeh, R., Mangalam, S., Mapoma, C.C., Marape, M., Marcenes, W., Margolis, D.J., Margono, C., Marks, G.B., Martin, R.V., Marzan, M.B., Mashal, M.T., Masiye, F., Mason-Jones, A.J., Matsushita, K., Matzopoulos, R., Mayosi, B.M., Mazorodze, T.T., McKay, A.C., McKee, M., McLain, A., Meaney, P.A., Medina, C., Mehndiratta, M.M., Mejia-Rodriguez, F., Mekonnen, W., Melaku, Y.A., Meltzer, M., Memish, Z.A., Mendoza, W., Mensah, G.A., Meretoja, A., Mhimbira, F.A., Micha, R., Miller, T.R., Mills, E.J., Misganaw, A., Mishra, S., Mohamed Ibrahim, N., Mohammad, K.A., Mokdad, A.H., Mola, G.L., Monasta, L., Montanez Hernandez, J.C., Montico, M., Moore, A.R., Morawska, L., Mori, R., Moschandreas, J., Moturi, W.N., Mozaffarian, D., Mueller, U.O., Mukaigawara, M., Mullany, E.C., Murthy, K.S., Naghavi, M., Nahas, Z., Naheed, A., Naidoo, K.S., Naldi, L., Nand, D., Nangia, V., Narayan, K.M., Nash, D., Neal, B., Nejjari, C., Neupane, S.P., Newton, C.R., Ngalesoni, F.N., Ngirabega Jde, D., Nguyen, G., Nguyen, N.T., Nieuwenhuijsen, M.J., Nisar, M.I., Nogueira, J.R., Nolla, J.M., Nolte, S., Norheim, O.F., Norman, R.E., Norrving, B., Nyakarahuka, L., Oh, I.H., Ohkubo, T., Olusanya, B.O., Omer, S.B., Opio, J.N., Orozco, R., Pagcatipunan, R.S., Jr., Pain, A.W., Pandian, J.D., Panelo, C.I., Papachristou, C., Park, E.K., Parry, C.D., Paternina Caicedo, A.J., Patten, S.B., Paul, V.K., Pavlin, B.I., Pearce, N., Pedraza, L.S., Pedroza, A., Pejin Stokic, L., Pekericli, A., Pereira, D.M., Perez-Padilla, R., Perez-Ruiz, F., Perico, N., Perry, S.A., Pervaiz, A., Pesudovs, K., Peterson, C.B., Petzold, M., Phillips, M.R., Phua, H.P., Plass, D., Poenaru, D., Polanczyk, G.V., Polinder, S., Pond, C.D., Pope, C.A., Pope, D., Popova, S., Pourmalek, F., Powles, J., Prabhakaran, D., Prasad, N.M., Qato, D.M., Quezada, A.D., Quistberg, D.A., Racape, L., Rafay, A., Rahimi, K., Rahimi-Movaghar, V., Rahman, S.U., Raju, M., Rakovac, I., Rana, S.M., Rao, M., Razavi, H., Reddy, K.S., Refaat, A.H., Rehm, J., Remuzzi, G., Ribeiro, A.L., Riccio, P.M., Richardson, L., Riederer, A., Robinson, M., Roca, A., Rodriguez, A., Rojas-Rueda, D., Romieu, I., Ronfani, L., Room, R., Roy, N., Ruhago, G.M., Rushton, L., Sabin, N., Sacco, R.L., Saha, S., Sahathevan, R., Sahraian, M.A., Salomon, J.A., Salvo, D., Sampson, U.K., Sanabria, J.R., Sanchez, L.M., Sanchez-Pimienta, T.G., Sanchez-Riera, L., Sandar, L., Santos, I.S., Sapkota, A., Satpathy, M., Saunders, J.E., Sawhney, M., Saylan, M.I., Scarborough, P., Schmidt, J.C., Schneider, I.J., Schottker, B., Schwebel, D.C., Scott, J.G., Seedat, S., Sepanlou, S.G., Serdar, B., Servan-Mori, E.E., Shaddick, G., Shahraz, S., Levy, T.S., Shangguan, S., She, J., Sheikhbahaei, S., Shibuya, K., Shin, H.H., Shinohara, Y., Shiri, R., Shishani, K., Shiue, I., Sigfusdottir, I.D., Silberberg, D.H., Simard, E.P., Sindi, S., Singh, A., Singh, G.M., Singh, J.A., Skirbekk, V., Sliwa, K., Soljak, M., Soneji, S., Soreide, K., Soshnikov, S., Sposato, L.A., Sreeramareddy, C.T., Stapelberg, N.J., Stathopoulou, V., Steckling, N., Stein, D.J., Stein, M.B., Stephens, N., Stockl, H., Straif, K., Stroumpoulis, K., Sturua, L., Sunguya, B.F., Swaminathan, S., Swaroop, M., Sykes, B.L., Tabb, K.M., Takahashi, K., Talongwa, R.T., Tandon, N., Tanne, D., Tanner, M., Tavakkoli, M., Te Ao, B.J., Teixeira, C.M., Tellez Rojo, M.M., Terkawi, A.S., Texcalac-Sangrador, J.L., Thackway, S.V., Thomson, B., Thorne-Lyman, A.L., Thrift, A.G., Thurston, G.D., Tillmann, T., Tobollik, M., Tonelli, M., Topouzis, F., Towbin, J.A., Toyoshima, H., Traebert, J., Tran, B.X., Trasande, L., Trillini, M., Trujillo, U., Dimbuene, Z.T., Tsilimbaris, M., Tuzcu, E.M., Uchendu, U.S., Ukwaja, K.N., Uzun, S.B., van de Vijver, S., Van Dingenen, R., van Gool, C.H., van Os, J., Varakin, Y.Y., Vasankari, T.J., Vasconcelos, A.M., Vavilala, M.S., Veerman, L.J., Velasquez-Melendez, G., Venketasubramanian, N., Vijayakumar, L., Villalpando, S., Violante, F.S., Vlassov, V.V., Vollset, S.E., Wagner, G.R., Waller, S.G., Wallin, M.T., Wan, X., Wang, H., Wang, J., Wang, L., Wang, W., Wang, Y., Warouw, T.S., Watts, C.H., Weichenthal, S., Weiderpass, E., Weintraub, R.G., Werdecker, A., Wessells, K.R., Westerman, R., Whiteford, H.A., Wilkinson, J.D., Williams, H.C., Williams, T.N., Woldeyohannes, S.M., Wolfe, C.D., Wong, J.Q., Woolf, A.D., Wright, J.L., Wurtz, B., Xu, G., Yan, L.L., Yang, G., Yano, Y., Ye, P., Yenesew, M., Yentur, G.K., Yip, P., Yonemoto, N., Yoon, S.J., Younis, M.Z., Younoussi, Z., Yu, C., Zaki, M.E., Zhao, Y., Zheng, Y., Zhou, M., Zhu, J., Zhu, S., Zou, X., Zunt, J.R., Lopez, A.D., Vos, T., Murray, C.J. (2015): Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. In: Lancet (Lond), 2015, 386, S. 2287-2323

Friedrich, R., Kuhn, A., Bessagnet, B., Blesl, M., Bruchof, D., Cowie, H., Fantke, P. (2010): D 5.3.1/2 Methods and results of the HEIMTSA/INTARESE Common Case Study. HEIMTSA - Health and Environment Integrated Methodology and Toolbox for Scenario Development, www.integrated-assessment.eu/eu/sites/default/files/CCS_FINAL_REPORT_final.pdf

Fusar-Poli, P., Radua, J. (2018): Ten simple rules for conducting umbrella reviews. In: Evid Based Ment Health, 2018, 21, S. 95-100

Gao, W., Yuan, C., Zhang, J., Li, L., Yu, L., Wiegman, C.H., Barnes, P.J., Adcock, I.M., Huang, M., Yao, X. (2015): Klotho expression is reduced in COPD airway epithelial cells: effects on inflammation and oxidant injury. In: Clin Sci (Lond), 2015, 129, S. 1011-1023

Garfield, E. (1955): Citation indexes for science; a new dimension in documentation through association of ideas. In: Science (New York, NY), 1955, 122, S. 108-111

GBD 2015 Chronic Respiratory Disease Collaborators (2017): Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. In: The Lancet Respiratory medicine, 2017, 5, S. 691-706

GBD 2015 Risk Factors Collaborators (2016): Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. In: Lancet (London, England), 2016, 388, S. 1659-1724

GBD 2016 Risk Factors Collaborators (2017): Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. In: Lancet (Lond), 2017, 390, S. 1345-1422

GBD 2017 Risk Factor Collaborators (2018): Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. In: Lancet (Lond), 2018, 392, S. 1923-1994

GBD 2019 Risk Factors Collaborators (2020): Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. In: Lancet (Lond), 2020, 396, S. 1223-1249

GBD Chronic Respiratory Disease Collaborators (2020): Prevalence and attributable health burden of chronic respiratory diseases, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. In: Lancet Respir Med, 2020, 8, S. 585-596

Gong, H., Jr., Shamoo, D.A., Anderson, K.R., Linn, W.S. (1997): Responses of older men with and without chronic obstructive pulmonary disease to prolonged ozone exposure. In: Arch Environ Health, 1997, 52, S. 18-25

Goodman, J.E., Prueitt, R.L., Sax, S.N., Bailey, L.A., Rhomberg, L.R. (2013): Evaluation of the causal framework used for setting National Ambient Air Quality Standards. In: Crit Rev Toxicol, 2013, 43, S. 829-849

Goodman, J.E., Prueitt, R.L., Sax, S.N., Lynch, H.N., Zu, K., Lemay, J.C., King, J.M., Venditti, F.J. (2014): Weight-of-evidence evaluation of short-term ozone exposure and cardiovascular effects. In: Crit Rev Toxicol, 2014, 44, S. 725-790

Goodman, J.E., Prueitt, R.L., Sax, S.N., Pizzurro, D.M., Lynch, H.N., Zu, K., Venditti, F.J. (2015): Ozone exposure and systemic biomarkers: Evaluation of evidence for adverse cardiovascular health impacts. In: Crit Rev Toxicol, 2015, 45, S. 412-452

Goodman, J.E., Zu, K., Loftus, C.T., Lynch, H.N., Prueitt, R.L., Mohar, I., Shubin, S.P., Sax, S.N. (2018): Short-term ozone exposure and asthma severity: Weight-of-evidence analysis. In: Environ Res, 2018, 160, S. 391-397

Grant, M.J., Booth, A. (2009): A typology of reviews: an analysis of 14 review types and associated methodologies. In: Health Info Libr J, 2009, 26, S. 91-108

Guo, L.Q., Chen, Y., Mi, B.B., Dang, S.N., Zhao, D.D., Liu, R., Wang, H.L., Yan, H. (2019): Ambient air pollution and adverse birth outcomes: a systematic review and meta-analysis. In: Journal of Zhejiang University Science B, 2019, 20, S. 238-252

Hänninen, O., Knol, A. (2011a): European Perspectives on Environmental Burden of Disease Estimates for Nine Stressors in Six European Countries. National Institute for Health and Welfare, Helsinki, https://www.julkari.fi/bitstream/handle/10024/79910/b75f6999-e7c4-4550-a939-3bccb19e41c1.pdf

Hänninen, O., Knol, A.B. (2011b): EBoDE-Report. Environmental Perspectives on Environmental Burden of Disease. Estimates for Nine Stressors in Six European Countries. National Institute for Health and Welfare, Helsinki, https://www.julkari.fi/bitstream/handle/10024/79910/b75f6999-e7c4-4550-a939-3bccb19e41c1.pdf

Hänninen, O., Knol, A.B., Jantunen, M., Lim, T.A., Conrad, A., Rappolder, M., Carrer, P., Fanetti, A.C., Kim, R., Buekers, J., Torfs, R., Iavarone, I., Classen, T., Hornberg, C., Mekel, O.C. (2014): Environmental burden of disease in Europe: assessing nine risk factors in six countries. In: Environ Health Perspect, 2014, 122, S. 439-446

Hänninen, O., Lehtomäki, H., Korhonen, A., Rumrich, I., Asikainen, A. (2016): Characterizing the Health Risks Attributable to Tropospheric Ozone in Finland. In: JSM Environ Sci Ecol 2016, 4, 1023

Hardaker, L., Bahra, P., de Billy, B.C., Freeman, M., Kupfer, N., Wyss, D., Trifilieff, A. (2012): The ion channel transient receptor potential melastatin-2 does not play a role in inflammatory mouse models of chronic obstructive pulmonary diseases. In: Respir Res, 2012, 13, S. 30

Health Council of the Netherlands (2018): Health benefits through cleaner air. Health Council of the Netherlands, The Hague, https://www.healthcouncil.nl/binaries/healthcouncil/documents/advisory-reports/2018/01/23/health-benefits-through-cleaner-air/health_benefits_through_cleaner_air_0.pdf

Hehua, Z., Qing, C., Shanyan, G., Qijun, W., Yuhong, Z. (2017): The impact of prenatal exposure to air pollution on childhood wheezing and asthma: A systematic review. In: Environ Res, 2017, 159, S. 519-530

Heroux, M.E., Anderson, H.R., Atkinson, R., Brunekreef, B., Cohen, A., Forastiere, F., Hurley, F., Katsouyanni, K., Krewski, D., Krzyzanowski, M., Kunzli, N., Mills, I., Querol, X., Ostro, B., Walton, H. (2015): Quantifying the health impacts of ambient air pollutants: recommendations of a WHO/Europe project. In: Int J Public Health, 2015, 60, S. 619-627

Hicks, A., Goodnow, R., Jr., Cavallo, G., Tannu, S.A., Ventre, J.D., Lavelle, D., Lora, J.M., Satjawatcharaphong, J., Brovarney, M., Dabbagh, K., Tare, N.S., Oh, H., Lamb, M., Sidduri, A., Dominique, R., Qiao, Q., Lou, J.P., Gillespie, P., Fotouhi, N., Kowalczyk, A., Kurylko, G., Hamid, R., Wright, M.B., Pamidimukkala, A., Egan, T., Gubler, U., Hoffman, A.F., Wei, X., Li, Y.L., O'Neil, J., Marcano, R., Pozzani, K., Molinaro, T., Santiago, J., Singer, L., Hargaden, M., Moore, D., Catala, A.R., Chao, L.C., Benson, J., March, T., Venkat, R., Mancebo, H., Renzetti, L.M. (2010a): Effects of LTB4 receptor antagonism on pulmonary inflammation in rodents and non-human primates. In: Prostaglandins Other Lipid Mediat, 2010a, 92, S. 33-43

Hicks, A., Kourteva, G., Hilton, H., Li, H., Lin, T.A., Liao, W., Li, Y., Wei, X., March, T., Benson, J., Renzetti, L.M. (2010b): Cellular and molecular characterization of ozone-induced pulmonary inflammation in the Cynomolgus monkey. In: Inflammation, 2010b, 33, S. 144-156

Hiltermann, T.J., Peters, E.A., Alberts, B., Kwikkers, K., Borggreven, P.A., Hiemstra, P.S., Dijkman, J.H., van Bree, L.A., Stolk, J. (1998): Ozone-induced airway hyperresponsiveness in patients with asthma: role of neutrophil-derived serine proteinases. In: Free radical biology & medicine, 1998, 24, S. 952-958

Hoek, G., Verhoeff, A., Fisher, P. (1997): Daily mortality and air pollution in the Netherlands, 1986-1994. Agricultural University Wageningen, Wageningen

Hofstetter, P. (1998): Perspectives in Life Cycle Impact Assessment: A Structured Approach to Combine Models of the Technosphere, Ecosphere and Valuesphere. 1. Auflage, Springer Science + Business media, New York

Holz, O., Biller, H., Mueller, M., Kane, K., Rosano, M., Hanrahan, J., Hava, D.L., Hohlfeld, J.M. (2015): Efficacy and safety of inhaled calcium lactate PUR118 in the ozone challenge model -a clinical trial. In: BMC Pharmacol Toxicol, 2015, 16, S. 21

Holz, O., Khalilieh, S., Ludwig-Sengpiel, A., Watz, H., Stryszak, P., Soni, P., Tsai, M., Sadeh, J., Magnussen, H. (2010): SCH527123, a novel CXCR2 antagonist, inhibits ozone-induced neutrophilia in healthy subjects. In: Eur Respir J, 2010, 35, S. 564-570

Hornberg, C., Claßen, T., Steckling, N., Samson, R., McCall, T., Tobollik, M., Mekel, O., Terschüren, C., Schillmöller, Z., Popp, J., Paetzelt, G., Schümann, M. (2013): Quantifizierung der Auswirkungen verschiedener Umweltbelastungen auf die Gesundheit der Menschen in Deutschland unter Berücksichtigung der bevölkerungsbezogenen Expositionsermittlung (Verteilungsbasierte Analyse gesundheitlicher Auswirkungen von Umwelt-Stressoren, VegAS). Umweltbundesamt (UBA), Dessau-Roßlau, http://www.umweltbundesamt.de/vegas-studie

Hornberg, C., Steckling, N., Tobollik, M., Mertes, H., Gerullis, M., Claßen, T., Schillmöller, Z., Popp, J., Paetzelt, G., Roos-Bugiel, J. (2014): Das Environmental Burden of Disease (EBD)-Konzept und Gesundheitskostenanalysen als Instrumente zur Prioritätensetzung im gesundheitsbezogenen Umweltschutz (Gesundheitsökonomie und Environmental Burden of Disease im Umwelt-Schutz, GEniUS). Umweltbundesamt (UBA), Dessau-Roßlau, http://www.bmub.bund.de/fileadmin/Daten_BMU/Pools/Forschungsdatenbank/fkz_3711_62_241_3_gesundheitsbezogenen_umweltschutz_bf.pdf

Houthuijs, D., de Leeuw, F. (2018): Combined health impact assessment of noise and air quality in urban agglomerations. An explorative study. European Topic Centre on Air Pollution and Climate Change Mitigation (ETC/ACM), Bilthoven, https://www.eionet.europa.eu/etcs/etc-atni/products/etc-atni-reports/etcacm_tp_2017_12_hia_end_aggloms/@@download/file/ETCACM_TP_2017_12_HIA_END_aggloms.pdf

Howarth, A., Pearce, E., Ozdemiroglu, E., Seccombe-Hett, T., Wieringa, K., Streefkerk, C., de Hollander, A. (2001): Valuing the benefits of environmental policy. National Institute of Public Health and the Environment (RIVM), Bilthoven, https://www.rivm.nl/bibliotheek/rapporten/481505024.pdf

Hu, C.Y., Fang, Y., Li, F.L., Dong, B., Hua, X.G., Jiang, W., Zhang, H., Lyu, Y., Zhang, X.J. (2019): Association between ambient air pollution and Parkinson's disease: Systematic review and meta-analysis. In: Environ Res, 2019, 168, S. 448-459

Hu, H., Ha, S., Roth, J., Kearney, G., Talbott, E.O., Xu, X. (2014): Ambient Air Pollution and Hypertensive Disorders of Pregnancy: A Systematic Review and Meta-analysis. In: Atmos Environ, 2014, 97, S. 336-345

Hurley, F., Hunt, A., Cowie, H., Holland, M., Miller, B., Pye, S., Watkiss, P. (2005a): Methodology Paper (Volume 2) for Service Contract for carrying out cost-benefit analysis of air quality related issues, in particular in the clean air for Europe (CAFE) programme. AEA Technology Environment, Didcot, http://www.cafecba.org/assets/volume_2_methodology_overview_02-05.pdf

Hurley, F., Hunt, A., Cowie, H., Holland, M., Miller, B., Pye, S., Watkiss, P. (2005b): Service Contract for Carrying out Cost-Benefit Analysis of Air Quality Related Issues, in Particular in the Clean Air for Europe (CAFE) Programme. AEA Technology Environment, Didcot, http://ec.europa.eu/environment/archives/cafe/pdf/cba_methodology_vol2.pdf

India State-Level Disease Burden Initiative Air Pollution Collaborators (2019): The impact of air pollution on deaths, disease burden, and life expectancy across the states of India: the Global Burden of Disease Study 2017. In: Lancet Planet Health, 2019, 3, S. e26-e39

James, K.L., Randall, N.P., Haddaway, N.R. (2016): A methodology for systematic mapping in environmental sciences. In: Environ Evid 2016, 5, S. 1-13

Jerrett, M., Burnett, R.T., Pope, C.A., 3rd, Ito, K., Thurston, G., Krewski, D., Shi, Y., Calle, E., Thun, M. (2009): Long-term ozone exposure and mortality. In: N Engl J Med, 2009, 360, S. 1085-1095

Ji, M., Cohan, D.S., Bell, M.L. (2011): Meta-analysis of the Association between Short-Term Exposure to Ambient Ozone and Respiratory Hospital Admissions. In: Environ Res Lett, 2011, 6, S. 024006

Johnson, D.A. (1987): Effects of ozone and nitrogen dioxide on human lung proteinase inhibitors. In: Res Rep Health Eff Inst, 1987, 11, S. 5-25

Jurewicz, J., Dziewirska, E., Radwan, M., Hanke, W. (2018): Air pollution from natural and anthropic sources and male fertility. In: Reprod Biol Endocrinol, 2018, 16, S. 109

Kallweit, D., Wintermeyer, D. (2013): Berechnung der gesundheitlichen Belastung der Bevölkerung in Deutschland durch Feinstaub (PM10). In: UMID, 2013, 4, S. 18-24

Kasdagli, M.I., Katsouyanni, K., Dimakopoulou, K., Samoli, E. (2019): Air pollution and Parkinson's disease: A systematic review and meta-analysis up to 2018. In: Int J Hyg Environ Health, 2019, 222, S. 402-409

Katsouyanni, K., Samet, J.M., Anderson, H.R., Atkinson, R., Le Tertre, A., Medina, S., Samoli, E., Touloumi, G., Burnett, R.T., Krewski, D., Ramsay, T., Dominici, F., Peng, R.D., Schwartz, J., Zanobetti, A. (2009): Air pollution and health: a European and North American approach (APHENA). In: Res Rep Health Eff Inst, 2009, 142, S. 5-90

Kazemiparkouhi, F., Eum, K.D., Wang, B., Manjourides, J., Suh, H.H. (2019): Long-term ozone exposures and cause-specific mortality in a US Medicare cohort. In: J Expo Sci Environ Epidemiol, 2019, 30, S. 650-658

Kehrl, H.R., Hazucha, M.J., Solic, J.J., Bromberg, P.A. (1985): Responses of subjects with chronic obstructive pulmonary disease after exposures to 0.3 ppm ozone. In: Am Rev Respir Dis, 1985, 13, S. 719-724

Kierstein, S., Poulain, F.R., Cao, Y., Grous, M., Mathias, R., Kierstein, G., Beers, M.F., Salmon, M., Panettieri, R.A., Jr., Haczku, A. (2006): Susceptibility to ozone-induced airway inflammation is associated with decreased levels of surfactant protein D. In: Respir Res, 2006, 7, S. 85

King, C., Kirkham, J., Hawcutt, D., Sinha, I. (2018): The effect of outdoor air pollution on the risk of hospitalisation for bronchiolitis in infants: a systematic review. In: PeerJ, 2018, 6, S. e5352

Kirkham, P.A., Caramori, G., Casolari, P., Papi, A.A., Edwards, M., Shamji, B., Triantaphyllopoulos, K., Hussain, F., Pinart, M., Khan, Y., Heinemann, L., Stevens, L., Yeadon, M., Barnes, P.J., Chung, K.F., Adcock, I.M. (2011): Oxidative stress-induced antibodies to carbonyl-modified protein correlate with severity of chronic obstructive pulmonary disease. In: Am J Respir Crit Care Med, 2011, 184, S. 796-802

Kirsten, A., Watz, H., Kretschmar, G., Pedersen, F., Bock, D., Meyer-Sabellek, W., Magnussen, H. (2011): Efficacy of the pan-selectin antagonist Bimosiamose on ozone-induced airway inflammation in healthy subjects--a double blind, randomized, placebo-controlled, cross-over clinical trial. In: Pulm Pharmacol Ther, 2011, 24, S. 555-558

Klemm, R.J., Thomas, E.L., Wyzga, R.E. (2011): The impact of frequency and duration of air quality monitoring: Atlanta, GA, data modeling of air pollution and mortality. In: J Air Waste Manag Assoc, 2011, 61, S. 1281-1291

Knippschild, S., Baulig, C., Krummenauer, F. (2015): Heterogenität in Meta-Analysen – kein Vergleich von Äpfeln und Birnen erlaubt … [Heterogeneity in meta-analysis – do not compare apples and oranges …]. In: Z Zahnärztl Impl, 2015, 31, S. 224-229

Knol, A., Staatsen, B. (2005): Trends in the environmental burden of disease in the Netherlands 1980 – 2020. National Institute of Public Health and the Environment (RIVM), Bilthoven, https://www.rivm.nl/bibliotheek/rapporten/500029001.pdf

Kobayashi, Y., Peters, G.M., Ashbolt, N.J., Shiels, S., Khan, S.J. (2015): Assessing burden of disease as disability adjusted life years in life cycle assessment. In: Sci Total Environ, 2015, 530-531, S. 120-128

Koman, P.D., Hogan, K.A., Sampson, N., Mandell, R., Coombe, C.M., Tetteh, M.M., Hill-Ashford, Y.R., Wilkins, D., Zlatnik, M.G., Loch-Caruso, R., Schulz, A.J., Woodruff, T.J. (2018): Examining Joint Effects of Air Pollution Exposure and Social Determinants of Health in Defining "At-Risk" Populations Under the Clean Air Act: Susceptibility of Pregnant Women to Hypertensive Disorders of Pregnancy. In: World Med Health Policy, 2018, 10, S. 7-54

Kramer, U., Behrendt, H. (2019): [Air pollution and atopic eczema : Systematic review of findings from environmental epidemiological studies]. In: Hautarzt, 2019, 70, S. 169-184

Lafuente, R., Garcia-Blaquez, N., Jacquemin, B., Checa, M.A. (2016): Outdoor air pollution and sperm quality. In: Fertil Steril, 2016, 106, S. 880-896

Lai, H.K., Tsang, H., Wong, C.M. (2013): Meta-analysis of adverse health effects due to air pollution in Chinese populations. In: BMC public health, 2013, 13, S. 360

Lazaar, A.L., Sweeney, L.E., MacDonald, A.J., Alexis, N.E., Chen, C., Tal-Singer, R. (2011): SB-656933, a novel CXCR2 selective antagonist, inhibits ex vivo neutrophil activation and ozone-induced airway inflammation in humans. In: Br J Clin Pharmacol, 2011, 72, S. 282-293

Lehtomaki, H., Korhonen, A., Asikainen, A., Karvosenoja, N., Kupiainen, K., Paunu, V.V., Savolahti, M., Sofiev, M., Palamarchuk, Y., Karppinen, A., Kukkonen, J., Hanninen, O. (2018): Health Impacts of Ambient Air Pollution in Finland. In: Int J Environ Res Public Health, 2018, 15, S. 736

LfU (2018): Faktenblatt OzonAugsburg: Bayerisches Landesamt für Umwelt (LfU), Augsburg, https://www.lfu.bayern.de/luft/doc/ozoninfo.pdf

LfU (2020): Bodennahes Ozon und SommersmogAugsburg: Bayerisches Landesamt für Umwelt (LfU), Augsburg, https://www.lfu.bayern.de/buerger/doc/uw_47_bodennahes_ozon.pdf

Li, C., Fang, D., Xu, D., Wang, B., Zhao, S., Yan, S., Wang, Y. (2014): Main air pollutants and diabetes-associated mortality: a systematic review and meta-analysis. In: Eur J Endocrinol, 2014, 171, S. R183-190

Li, F., Wiegman, C., Seiffert, J.M., Zhu, J., Clarke, C., Chang, Y., Bhavsar, P., Adcock, I., Zhang, J., Zhou, X., Chung, K.F. (2013): Effects of N-acetylcysteine in ozone-induced chronic obstructive pulmonary disease model. In: PloS one, 2013, 8, S. e80782

Li, F., Zhang, P., Zhang, M., Liang, L., Sun, X., Li, M., Tang, Y., Bao, A., Gong, J., Zhang, J., Adcock, I., Chung, K.F., Zhou, X. (2016a): Hydrogen Sulfide Prevents and Partially Reverses Ozone-Induced Features of Lung Inflammation and Emphysema in Mice. In: Am J Respir Cell Mol Biol, 2016a, 55, S. 72-81

Li, J., Sun, S., Tang, R., Qiu, H., Huang, Q., Mason, T.G., Tian, L. (2016b): Major air pollutants and risk of COPD exacerbations: a systematic review and meta-analysis. In: Int J Chron Obstruct Pulmon Dis, 2016b, 11, S. 3079-3091

Li, J., Woodward, A., Hou, X.Y., Zhu, T., Zhang, J., Brown, H., Yang, J., Qin, R., Gao, J., Gu, S., Li, J., Xu, L., Liu, X., Liu, Q. (2017a): Modification of the effects of air pollutants on mortality by temperature: A systematic review and meta-analysis. In: Sci Total Environ, 2017a, 575, S. 1556-1570

Li, R., Jiang, N., Liu, Q., Huang, J., Guo, X., Liu, F., Gao, Z. (2017b): Impact of Air Pollutants on Outpatient Visits for Acute Respiratory Outcomes. In: Int J Environ Res Public Health, 2017b, 14, S. 47

Li, K., Rollins, J., Yan, E. (2018a): Web of Science use in published research and review papers 1997-2017: a selective, dynamic, cross-domain, content-based analysis. In: Scientometrics, 2018a, 115, S. 1-20

Li, X., Michaeloudes, C., Zhang, Y.L., Wiegman, C.H., Adcock, I.M., Lian, Q.Z., Mak, J.C.W., Bhavsar, P.K., Chung, K.F. (2018b): Mesenchymal stem cells alleviate oxidative stress-induced mitochondrial dysfunction in the airways. In: J Allergy Clin Immunol, 2018b, 141, S. 1634-1645.e5

Lim, C.C., Hayes, R.B., Ahn, J., Shao, Y., Silverman, D.T., Jones, R.R., Garcia, C., Bell, M.L., Thurston, G.D. (2019): Long-Term Exposure to Ozone and Cause-Specific Mortality Risk in the United States. In: Am J Respir Crit Care Med, 2019, 200, S. 1022-1031

Lim, S.S., Vos, T., Flaxman, A.D., Danaei, G., Shibuya, K., Adair-Rohani, H., Amann, M., Anderson, H.R., Andrews, K.G., Aryee, M., Atkinson, C., Bacchus, L.J., Bahalim, A.N., Balakrishnan, K., Balmes, J., Barker-Collo, S., Baxter, A., Bell, M.L., Blore, J.D., Blyth, F., Bonner, C., Borges, G., Bourne, R., Boussinesq, M., Brauer, M., Brooks, P., Bruce, N.G., Brunekreef, B., Bryan-Hancock, C., Bucello, C., Buchbinder, R., Bull, F., Burnett, R.T., Byers, T.E., Calabria, B., Carapetis, J., Carnahan, E., Chafe, Z., Charlson, F., Chen, H., Chen, J.S., Cheng, A.T., Child, J.C., Cohen, A., Colson, K.E., Cowie, B.C., Darby, S., Darling, S., Davis, A., Degenhardt, L., Dentener, F., Des Jarlais, D.C., Devries, K., Dherani, M., Ding, E.L., Dorsey, E.R., Driscoll, T., Edmond, K., Ali, S.E., Engell, R.E., Erwin, P.J., Fahimi, S., Falder, G., Farzadfar, F., Ferrari, A., Finucane, M.M., Flaxman, S., Fowkes, F.G., Freedman, G., Freeman, M.K., Gakidou, E., Ghosh, S., Giovannucci, E., Gmel, G., Graham, K., Grainger, R., Grant, B., Gunnell, D., Gutierrez, H.R., Hall, W., Hoek, H.W., Hogan, A., Hosgood, H.D., 3rd, Hoy, D., Hu, H., Hubbell, B.J., Hutchings, S.J., Ibeanusi, S.E., Jacklyn, G.L., Jasrasaria, R., Jonas, J.B., Kan, H., Kanis, J.A., Kassebaum, N., Kawakami, N., Khang, Y.H., Khatibzadeh, S., Khoo, J.P., Kok, C., Laden, F., Lalloo, R., Lan, Q., Lathlean, T., Leasher, J.L., Leigh, J., Li, Y., Lin, J.K., Lipshultz, S.E., London, S., Lozano, R., Lu, Y., Mak, J., Malekzadeh, R., Mallinger, L., Marcenes, W., March, L., Marks, R., Martin, R., McGale, P., McGrath, J., Mehta, S., Mensah, G.A., Merriman, T.R., Micha, R., Michaud, C., Mishra, V., Mohd Hanafiah, K., Mokdad, A.A., Morawska, L., Mozaffarian, D., Murphy, T., Naghavi, M., Neal, B., Nelson, P.K., Nolla, J.M., Norman, R., Olives, C., Omer, S.B., Orchard, J., Osborne, R., Ostro, B., Page, A., Pandey, K.D., Parry, C.D., Passmore, E., Patra, J., Pearce, N., Pelizzari, P.M., Petzold, M., Phillips, M.R., Pope, D., Pope, C.A., 3rd, Powles, J., Rao, M., Razavi, H., Rehfuess, E.A., Rehm, J.T., Ritz, B., Rivara, F.P., Roberts, T., Robinson, C., Rodriguez-Portales, J.A., Romieu, I., Room, R., Rosenfeld, L.C., Roy, A., Rushton, L., Salomon, J.A., Sampson, U., Sanchez-Riera, L., Sanman, E., Sapkota, A., Seedat, S., Shi, P., Shield, K., Shivakoti, R., Singh, G.M., Sleet, D.A., Smith, E., Smith, K.R., Stapelberg, N.J., Steenland, K., Stockl, H., Stovner, L.J., Straif, K., Straney, L., Thurston, G.D., Tran, J.H., Van Dingenen, R., van Donkelaar, A., Veerman, J.L., Vijayakumar, L., Weintraub, R., Weissman, M.M., White, R.A., Whiteford, H., Wiersma, S.T., Wilkinson, J.D., Williams, H.C., Williams, W., Wilson, N., Woolf, A.D., Yip, P., Zielinski, J.M., Lopez, A.D., Murray, C.J., Ezzati, M., AlMazroa, M.A., Memish, Z.A. (2012): A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. In: Lancet (Lond), 2012, 380, S. 2224-2260

Lin, S., Liu, X., Le, L.H., Hwang, S.-A. (2008): Chronic exposure to ambient ozone and asthma hospital admissions among children. In: Environ Health Perspect, 2008, 116, S. 1725-1730

Linn, W.S., Fischer, D.A., Medway, D.A., Anzar, U.T., Spier, C.E., Valencia, L.M., Venet, T.G., Hackney, J.D. (1982): Short-term respiratory effects of 0.12 ppm ozone exposure in volunteers with chronic obstructive pulmonary disease. In: Am Rev Respir Dis, 1982, 125, S. 658-663

Linn, W.S., Shamoo, D.A., Venet, T.G., Spier, C.E., Valencia, L.M., Anzar, U.T., Hackney, J.D. (1983): Response to ozone in volunteers with chronic obstructive pulmonary disease. In: Arch Environ Health, 1983, 38, S. 278-283

Lipsett, M.J., Ostro, B.D., Reynolds, P., Goldberg, D., Hertz, A., Jerrett, M., Smith, D.F., Garcia, C., Chang, E.T., Bernstein, L. (2011): Long-term exposure to air pollution and cardiorespiratory disease in the California teachers study cohort. In: Am J Respir Crit Care Med, 2011, 184, S. 828-835

Liu, J.Y., Mao, F.R., Mao, Z.F., Wang, F.J., Zhu, Y.L., Wang, H.J. (2016): Emodin inhibited ozone stress-induced airway hyperresponsiveness by regulating epithelial protection mechanisms against injury. In: Int J Clin Exp Med, 2016, 9, S. 17404-17411

Logue, J.M., Price, P.N., Sherman, M.H., Singer, B.C. (2012): A method to estimate the chronic health impact of air pollutants in U.S. residences. In: Environ Health Perspect, 2012, 120, S. 216-222

Lumb, A. (2017). Smoking and Air Pollution. In: Lumb, A. (Hrsg.): Nunn's Applied Respiratory Physiology. 8. Auflage, Elsevier, Osford, 19. Kapitel

Luong, L.M.T., Sly, P.D., Thai, P.K., Phung, D. (2019): Impact of ambient air pollution and wheeze-associated disorders in children in Southeast Asia: a systematic review and meta-analysis. In: Rev Environ Health, 2019, 34, S. 125-139

Malig, B.J., Pearson, D.L., Chang, Y.B., Broadwin, R., Basu, R., Green, R.S., Ostro, B. (2016): A Time-Stratified Case-Crossover Study of Ambient Ozone Exposure and Emergency Department Visits for Specific Respiratory Diagnoses in California (2005-2008). In: Environ Health Perspect, 2016, 124, S. 745-753

Malley, C.S., Henze, D.K., Kuylenstierna, J.C.I., Vallack, H.W., Davila, Y., Anenberg, S.C., Turner, M.C., Ashmore, M.R. (2017): Updated Global Estimates of Respiratory Mortality in Adults ⩾30Years of Age Attributable to Long-Term Ozone Exposure. In: Environ Health Perspect, 2017, 125, S. 087021

March, T.H., Barr, E.B., Finch, G.L., Nikula, K.J., Seagrave, J.C. (2002): Effects of concurrent ozone exposure on the pathogenesis of cigarette smoke-induced emphysema in B6C3F1 mice. In: Inhal Toxicol, 2002, 14, S. 1187-1213

Martenies, S.E. (2017): Health and Inequality Metrics for Urban-scale Air Quality Management. University of Michigan, Michigan, https://deepblue.lib.umich.edu/handle/2027.42/138781

Martenies, S.E., Milando, C.W., Williams, G.O., Batterman, S.A. (2017): Disease and Health Inequalities Attributable to Air Pollutant Exposure in Detroit, Michigan. In: Int J Environ Res Public Health, 2017, 14, S. 1243

Miake-Lye, I.M., Hempel, S., Shanman, R., Shekelle, P.G. (2016): What is an evidence map? A systematic review of published evidence maps and their definitions, methods, and products. In: Syst Rev, 2016, 5, S. 28

Michaudel, C., Fauconnier, L., Jule, Y., Ryffel, B. (2018): Functional and morphological differences of the lung upon acute and chronic ozone exposure in mice. In: Sci Rep, 2018, 8, S. 10611

Miller, D.B., Karoly, E.D., Jones, J.C., Ward, W.O., Vallanat, B.D., Andrews, D.L., Schladweiler, M.C., Snow, S.J., Bass, V.L., Richards, J.E., Ghio, A.J., Cascio, W.E., Ledbetter, A.D., Kodavanti, U.P. (2015): Inhaled ozone (O3)-induces changes in serum metabolomic and liver transcriptomic profiles in rats. In: Toxicol Appl Pharmacol, 2015, 286, S. 65-79

Miller, D.B., Ghio, A.J., Karoly, E.D., Bell, L.N., Snow, S.J., Madden, M.C., Soukup, J., Cascio, W.E., Gilmour, M.I., Kodavanti, U.P. (2016a): Ozone Exposure Increases Circulating Stress Hormones and Lipid Metabolites in Humans. In: Am J Respir Crit Care Med, 2016a, 193, S. 1382-1391

Miller, D.B., Snow, S.J., Henriquez, A., Schladweiler, M.C., Ledbetter, A.D., Richards, J.E., Andrews, D.L., Kodavanti, U.P. (2016b): Systemic metabolic derangement, pulmonary effects, and insulin insufficiency following subchronic ozone exposure in rats. In: Toxicol Appl Pharmacol, 2016b, 306, S. 47-57

Minelli, C., Wei, I., Sagoo, G., Jarvis, D., Shaheen, S., Burney, P. (2011): Interactive Effects of Antioxidant Genes and Air Pollution on Respiratory Function and Airway Disease: A HuGE Review. In: Am J Epidemiol, 2011, 173, S. 603-620

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G. (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. In: PLoS Med, 2009, 6, S. e1000097

Moore, E., Chatzidiakou, L., Kuku, M.O., Jones, R.L., Smeeth, L., Beevers, S., Kelly, F.J., Barratt, B., Quint, J.K. (2016): Global Associations between Air Pollutants and Chronic Obstructive Pulmonary Disease Hospitalizations. A Systematic Review. In: Ann Am Thorac Soc, 2016, 13, S. 1814-1827

Murray, C., Lopez, A. (1996): The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. World Health Organization, World Bank, Harvard School of Public Health, Harvard, https://apps.who.int/iris/handle/10665/41864

Murray, C.J., Ezzati, M., Flaxman, A.D., Lim, S., Lozano, R., Michaud, C., Naghavi, M., Salomon, J.A., Shibuya, K., Vos, T., Wikler, D., Lopez, A.D. (2012): GBD 2010: design, definitions, and metrics. In: Lancet (Lond), 2012a, 380, S. 2063-2066

Mustafic, H., Jabre, P., Caussin, C., Murad, M.H., Escolano, S., Tafflet, M., Perier, M.C., Marijon, E., Vernerey, D., Empana, J.P., Jouven, X. (2012): Main air pollutants and myocardial infarction: a systematic review and meta-analysis. In: JAMA, 2012, 307, S. 713-721

Nambu, Z., Yokoyama, E. (1985): Tolerance to ozone in emphysematous rats. In: Sangyo Igaku, 1985, 27, S. 105-109

Newell, K., Kartsonaki, C., Lam, K.B.H., Kurmi, O. (2018): Cardiorespiratory health effects of gaseous ambient air pollution exposure in low and middle income countries: a systematic review and meta-analysis. In: Environ Health, 2018, 17, S. 41

Nhung, N.T.T., Amini, H., Schindler, C., Kutlar Joss, M., Dien, T.M., Probst-Hensch, N., Perez, L., Kunzli, N. (2017): Short-term association between ambient air pollution and pneumonia in children: A systematic review and meta-analysis of time-series and case-crossover studies. In: Environ Pollut, 2017, 230, S. 1000-1008

NLM (2019): MEDLINE®: Description of the Database. U.S. National Library of Medicine (NLM), https://www.nlm.nih.gov/bsd/medline.html

NTP (2015): Systematic reviews. National Toxicology Program (NTP), US Department of Health and Human Services, Durham, https://www.niehs.nih.gov/health/materials/systematic_review_508.pdf

OECD (2008): OECD-Umweltausblick bis 2030. OECD Publishing, Paris, http://www.oecd.org/env/indicators-modelling-outlooks/40203598.pdf

OECD (2012): OECD Environmental Outlook to 2050. Organisation for Economic Co-operation and Development (OECD), Paris, https://read.oecd-ilibrary.org/environment/oecd-environmental-outlook-to-2050_9789264122246-en#page283

Orellano, P., Quaranta, N., Reynoso, J., Balbi, B., Vasquez, J. (2017): Effect of outdoor air pollution on asthma exacerbations in children and adults: Systematic review and multilevel meta-analysis. In: PloS one, 2017, 12, S. e0174050

Ostro, B. (2004): Outdoor air pollution: assessing the environmental burden of disease at national and local levels. World Health Organization, Geneva, https://apps.who.int/iris/handle/10665/42909

Parker, J.D., Akinbami, L.J., Woodruff, T.J. (2009): Air pollution and childhood respiratory allergies in the United States. In: Environ Health Perspect, 2009, 117, S. 140-147

Pedersen, M., Stayner, L., Slama, R., Sorensen, M., Figueras, F., Nieuwenhuijsen, M.J., Raaschou-Nielsen, O., Dadvand, P. (2014): Ambient air pollution and pregnancy-induced hypertensive disorders: a systematic review and meta-analysis. In: Hypertension, 2014, 64, S. 494-500

Peters, R., Ee, N., Peters, J., Booth, A., Mudway, I., Anstey, K.J. (2019): Air Pollution and Dementia: A Systematic Review. In: JAD, 2019, 70, Suppl 1, S. S145-S163

Pinart, M., Hussain, F., Shirali, S., Li, F., Zhu, J., Clark, A.R., Ammit, A.J., Chung, K.F. (2014): Role of mitogen-activated protein kinase phosphatase-1 in corticosteroid insensitivity of chronic oxidant lung injury. In: Eur J Pharmacol, 2014, 744, S. 108-114

Pinichka, C., Bundhamcharoen, K., Shibuya, K. (2015): Diseases Burden of Chronic Obstructive Pulmonary Disease (COPD) Attributable to Ground-Level Ozone in Thailand: Estimates Based on Surface Monitoring Measurements Data. In: Glob J Health Sci, 2015, 8, S. 1-13

Pope, C.A. 3rd (2007): Mortality effects of longer term exposures to fine particulate air pollution: review of recent epidemiological evidence. In: Inhal Toxicol, 2007, 19 Suppl 1, S. 33-38

Prueitt, R.L., Goodman, J.E. (2011): The Global Burden of Ozone on Respiratory Mortality: No Clear Evidence for Association. In: Environ Health Perspect, 2011, 119, S. 158

Prueitt, R.L., Lynch, H.N., Zu, K., Sax, S.N., Venditti, F.J., Goodman, J.E. (2014): Weight-of-evidence evaluation of long-term ozone exposure and cardiovascular effects. In: Crit Rev Toxicol, 2014, 44, S. 791-822

Prüss-Üstün, A., Mathers, C., Corvalán, C., Woodwards, A. (2003): Introduction and Methods: Assessing the Environmental Burden of Disease at National and Local Levels. World Health Organization (WHO), Geneva, https://www.who.int/quantifying_ehimpacts/publications/9241546204/en/

Prüss-Üstün, A., Wolf, J., Corvalán, C., Bos, R., Neira, M. (2016): Preventing disease through healthy environments. A global assessment of the burden of disease from environmental risks. Geneva: World Health Organization (WHO), Geneva, http://apps.who.int/iris/bitstream/10665/204585/1/9789241565196_eng.pdf

Pryor, S., Steyn, D. (1995): Hebdomadal and diurnal cycles in ozone time series from the Lower Fraser Valley, B.C. In: Atmos Environ, 1995, 29, S. 1007–1019

Rao, A., Ahmed, M.K., Taub, P.J., Mamoun, J.S. (2016): The Correlation between Maternal Exposure to Air Pollution and the Risk of Orofacial Clefts in Infants: a Systematic Review and Meta-Analysis. In: J Oral Maxillofac Res, 2016, 7, S. e2

Requia, W.J., Adams, M.D., Arain, A., Papatheodorou, S., Koutrakis, P., Mahmoud, M. (2018): Global Association of Air Pollution and Cardiorespiratory Diseases: A Systematic Review, Meta-Analysis, and Investigation of Modifier Variables. In: Am J Public Health, 2018, 108, S. S123-S130

Rodriguez-Villamizar, L.A., Berney, C., Villa-Roel, C., Ospina, M.B., Osornio-Vargas, A., Rowe, B.H. (2016): The role of socioeconomic position as an effect-modifier of the association between outdoor air pollution and children's asthma exacerbations: an equity-focused systematic review. In: Rev Environ Health, 2016, 31, S. 297-309

Rojas-Rueda, D., Vrijheid, M., Robinson, O., Gunn Marit, A., Grazuleviciene, R., Slama, R., Nieuwenhuijsen, M. (2019): Environmental Burden of Childhood Disease in Europe. In: Int J Environ Res Public Health, 2019, 16, S. 1084

Russell, K.E., Chung, K.F., Clarke, C.J., Durham, A.L., Mallia, P., Footitt, J., Johnston, S.L., Barnes, P.J., Hall, S.R., Simpson, K.D., Starkey, M.R., Hansbro, P.M., Adcock, I.M., Wiegman, C.H. (2016): The MIF Antagonist ISO-1 Attenuates Corticosteroid-Insensitive Inflammation and Airways Hyperresponsiveness in an Ozone-Induced Model of COPD. In: PloS one, 2016, 11, S. e0146102

Schmucker, C., Motschall, E., Antes, G., Meerpohl, J. (2013): Methoden des Evidence Mappings. Eine systematische Übersichtsarbeit. In: Bundesgesundheitsbl, 2013, 56, S. 1390-1397

Schneider, A., Cyrys, J., Breitner, S., Kraus, U., Peters, A., Diegmann, V., Neunhäuserer, L. (2018): Quantifizierung von umweltbedingten Krankheitslasten aufgrund der Stickstoffdioxid- Exposition in Deutschland. Umweltbundesamt (UBA), Dessau-Roßlau, https://www.umweltbundesamt.de/sites/default/files/medien/421/publikationen/abschlussbericht_no2_krankheitslast_final_2018_03_05.pdf

Shah, A.S., Langrish, J.P., Nair, H., McAllister, D.A., Hunter, A.L., Donaldson, K., Newby, D.E., Mills, N.L. (2013): Global association of air pollution and heart failure: a systematic review and meta-analysis. In: Lancet (Lond), 2013, 382, S. 1039-1048

Shah, A.S., Lee, K.K., McAllister, D.A., Hunter, A., Nair, H., Whiteley, W., Langrish, J.P., Newby, D.E., Mills, N.L. (2015a): Short term exposure to air pollution and stroke: systematic review and meta-analysis. In: BMJ, 2015a, 350, S. h1295

Shah, A.S.V., Lee, K.K., McAllister, D.A., Hunter, A., Nair, H., Whiteley, W., Langrish, J.P., Newby, D.E., Mills, N.L. (2015b): Short term exposure to air pollution and stroke: systematic review and meta-analysis. In: BMJ-British Medical Journal, 2015b, 350, S. h1295

Shah, P.S., Balkhair, T. (2011): Air pollution and birth outcomes: a systematic review. In: Environ Int, 2011, 37, S. 498-516

Shang, Y., Sun, Z., Cao, J., Wang, X., Zhong, L., Bi, X., Li, H., Liu, W., Zhu, T., Huang, W. (2013): Systematic review of Chinese studies of short-term exposure to air pollution and daily mortality. In: Environ Int, 2013, 54, S. 100-111

Shao, Q., Liu, T., Korantzopoulos, P., Zhang, Z., Zhao, J., Li, G. (2016): Association between air pollution and development of atrial fibrillation: A meta-analysis of observational studies. In: Heart Lung, 2016, 45, S. 557-562

Shea, B.J., Reeves, B.C., Wells, G., Thuku, M., Hamel, C., Moran, J., Moher, D., Tugwell, P., Welch, V., Kristjansson, E., Henry, D.A. (2017): AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. In: BMJ 2017, 358, S. j4008

Sherwood, R.L., Lippert, W.E., Goldstein, E. (1986): Effect of 0.64 ppm ozone on alveolar macrophage lysozyme levels in rats with chronic pulmonary bacterial infection. In: Environ Res, 1986, 41, S. 378-387

Siddika, N., Balogun, H.A., Amegah, A.K., Jaakkola, J.J. (2016): Prenatal ambient air pollution exposure and the risk of stillbirth: systematic review and meta-analysis of the empirical evidence. In: Occup Environ Med, 2016, 73, S. 573-581

Smith, K.R., Jerrett, M., Anderson, H.R., Burnett, R.T., Stone, V., Derwent, R., Atkinson, R.W., Cohen, A., Shonkoff, S.B., Krewski, D., Pope, C.A., 3rd, Thun, M.J., Thurston, G. (2009): Public health benefits of strategies to reduce greenhouse-gas emissions: health implications of short-lived greenhouse pollutants. In: Lancet (Lond), 2009, 374, S. 2091-2103

Solic, J.J., Hazucha, M.J., Bromberg, P.A. (1982): The acute effects of 0.2 ppm ozone in patients with chronic obstructive pulmonary disease. In: Am Rev Respir Dis, 1982, 125, S. 664-669

Song, X., Liu, Y., Hu, Y., Zhao, X., Tian, J., Ding, G., Wang, S. (2016): Short-Term Exposure to Air Pollution and Cardiac Arrhythmia: A Meta-Analysis and Systematic Review. In Int J Environ Res Public Health, 2016, 13, S. 642

Soriano, J.B., Abajobir, A.A., Abate, K.H., Abera, S.F., Agrawal, A., Ahmed, M.B., Aichour, A.N., Aichour, I., Aichour, M.T.E., Alam, K., Alam, N., Alkaabi, J.M., Al-Maskari, F., Alvis-Guzman, N., Amberbir, A., Amoako, Y.A., Ansha, M.G., Anto, J.M., Asayesh, H., Atey, T.M., Avokpaho, E., Barac, A., Basu, S., Bedi, N., Bensenor, I.M., Berhane, A., Beyene, A.S., Bhutta, Z.A., Biryukov, S., Boneya, D.J., Brauer, M., Carpenter, D.O., Casey, D., Christopher, D.J., Dandona, L., Dandona, R., Dharmaratne, S.D., Do, H.P., Fischer, F., Geleto, A., Ghoshal, A.G., Gillum, R.F., Ginawi, I.A.M., Gupta, V., Hay, S.I., Hedayati, M.T., Horita, N., Hosgood, H.D., Jakovljevic, M.B., James, S.L., Jonas, J.B., Kasaeian, A., Khader, Y.S., Khalil, I.A., Khan, E.A., Khang, Y.H., Khubchandani, J., Knibbs, L.D., Kosen, S., Koul, P.A., Kumar, G.A., Leshargie, C.T., Liang, X.F., Abd El Razek, H.M., Majeed, A., Malta, D.C., Manhertz, T., Marquez, N., Mehari, A., Mensah, G.A., Miller, T.R., Mohammad, K.A., Mohammed, K.E., Mohammed, S., Mokdad, A.H., Naghavi, M., Nguyen, C.T., Nguyen, G., Nguyen, Q.L., Nguyen, T.H., Ningrum, D.N.A., Nong, V.M., Obi, J.I., Odeyemi, Y.E., Ogbo, F.A., Oren, E., Mahesh, P.A., Park, E.K., Patton, G.C., Paulson, K., Qorbani, M., Quansah, R., Rafay, A., Rahman, M.H.U., Rai, R.K., Rawaf, S., Reinig, N., Safiri, S., Sarmiento-Suarez, R., Sartorius, B., Savic, M., Sawhney, M., Shigematsu, M., Smith, M., Tadese, F., Thurston, G.D., Topor-Madry, R., Tran, B.X., Ukwaja, K.N., van Boven, J.F.M., Vlassov, V.V., Vollset, S.E., Wan, X., Werdecker, A., Hanson, S.W., Yano, Y., Yimam, H.H., Yonemoto, N., Yu, C.H., Zaidi, Z., Zaki, M.E., Murray, C.J.L., Vos, T. (2017): Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. In: Lancet Resp Med, 2017, 5, S. 691-706

Srebotnjak, T., Porsch, L., Friedrich, R. (2015): Methodische Grundlagen des Environmental Burden of Disease (EBD)-Ansatzes der WHO zur quantitativen Bewertung von umweltbedingten Krankheitslasten – Chancen, Risiken und Grenzen der Methodik aus naturwissenschaftlicher, rechtlicher und ethischer Perspektive („EBDreview“). Umweltbundesamt (UBA), Berlin, https://www.umweltbundesamt.de/sites/default/files/medien/378/publikationen/umwelt_und_gesundheit_05_2015_methodische_grundlagen_des_environment_burden_disease-ansatzes.pdf

Statistische Ämter des Bundes und der Länder (2014): Einwohner 1991 bis 2018 (WZ 2008). Statistisxche Ämter des Bundes und der Länder, Wiesbaden, https://www.statistik-bw.de/VGRdL/tbls/tab.jsp?rev=RV2014&tbl=tab20&lang=de-DE

Statistische Ämter des Bundes und der Länder. (2018): Ergebnisse des Zensus 2011 zum Download – erweitert. Statistische Ämter des Bundes und der Länder, Wiesbaden, https://www.zensus2011.de/DE/Home/Aktuelles/DemografischeGrunddaten.html?nn=3065474

Stieb, D.M., Chen, L., Eshoul, M., Judek, S. (2012): Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. In: Environ Res, 2012, 117, S. 100-111

Stieb, D.M., Judek, S., Burnett, R.T. (2002): Meta-analysis of time-series studies of air pollution and mortality: effects of gases and particles and the influence of cause of death, age, and season. In: J Air Waste Manag Assoc, 2002, 52, S. 470-484

Strak, M., Janssen, N., Beelen, R., Schmitz, O., Karssenberg, D., Houthuijs, D., van den Brink, C., Dijst, M., Brunekreef, B., Hoek, G. (2017): Associations between lifestyle and air pollution exposure: Potential for confounding in large administrative data cohorts. In: Environ Res, 2017, 156, S. 364-373

Strickland, M.J., Darrow, L.A., Klein, M., Flanders, W.D., Sarnat, J.A., Waller, L.A., Sarnat, S.E., Mulholland, J.A., Tolbert, P.E. (2010): Short-term associations between ambient air pollutants and pediatric asthma emergency department visits. In: Am J Respir Crit Care Med, 2010, 182, S. 307-316

Sun, Z., Li, F., Zhou, X., Wang, W. (2017): Generation of a Chronic Obstructive Pulmonary Disease Model in Mice by Repeated Ozone Exposure. In: JoVE, 2017, 126, S. 56095

Tang, L., Wang, Q.Y., Cheng, Z.P., Hu, B., Liu, J.D., Hu, Y. (2016): Air pollution and venous thrombosis: a meta-analysis. In: Sci Rep, 2016, 6, S. 32794

Tang, Y.M., Liu, X.N., Zhang, Q.J., Pan, J.J., He, T.J., Li, Q., Yu, C.H., Zhang, L. (2018): Chronic obstructive pulmonary disease deaths, disability-adjusted life years, and risk factors in Hubei province of mid-China, 1990-2015: the Global Burden of Disease Study 2015. In: Public Health, 2018, 161, S. 12-19

Teng, T.H., Williams, T.A., Bremner, A., Tohira, H., Franklin, P., Tonkin, A., Jacobs, I., Finn, J. (2014): A systematic review of air pollution and incidence of out-of-hospital cardiac arrest. In: J Epidemiol Community Health, 2014, 68, S. 37-43

Thomson, E.M., Pal, S., Guenette, J., Wade, M.G., Atlas, E., Holloway, A.C., Williams, A., Vincent, R. (2016): Ozone Inhalation Provokes Glucocorticoid-Dependent and -Independent Effects on Inflammatory and Metabolic Pathways. In: Toxicol Sci, 2016, 152, S. 17-28

Thomson, E.M., Pilon, S., Guenette, J., Williams, A., Holloway, A.C. (2018): Ozone modifies the metabolic and endocrine response to glucose: Reproduction of effects with the stress hormone corticosterone. In: Toxicol Appl Pharmacol, 2018, 342, S. 31-38

Tian, Y., Liu, H., Zhao, Z., Xiang, X., Li, M., Juan, J., Song, J., Cao, Y., Wang, X., Chen, L., Wei, C., Hu, Y., Gao, P. (2018): Association between ambient air pollution and daily hospital admissions for ischemic stroke: A nationwide time-series analysis. In: PLoS Med, 2018, 15, S. e1002668

Tobollik, M., Plass, D., Steckling, N., Zeeb, H., Wintermeyer, D., Hornberg, C. (2018): Das Konzept der umweltbedingten Krankheitslast [The Environmental Burden of Disease Concept]. In: Gesundheitswesen, 2018, 80, S. 154-159

Toward, T.J., Broadley, K.J. (2002): Airway function, oedema, cell infiltration and nitric oxide generation in conscious ozone-exposed guinea-pigs: effects of dexamethasone and rolipram. In: Br J Pharmacol, 2002, 136, S. 735-745

Triantaphyllopoulos, K., Hussain, F., Pinart, M., Zhang, M., Li, F., Adcock, I., Kirkham, P., Zhu, J., Chung, K.F. (2011): A model of chronic inflammation and pulmonary emphysema after multiple ozone exposures in mice. In: Am J Physiol Lung Cell Mol Physiol, 2011, 300, S. L691-700

Turner, M.C., Jerrett, M., Pope, C.A., 3rd, Krewski, D., Gapstur, S.M., Diver, W.R., Beckerman, B.S., Marshall, J.D., Su, J., Crouse, D.L., Burnett, R.T. (2016): Long-Term Ozone Exposure and Mortality in a Large Prospective Study. In: Am J Respir Crit Care Med, 2016, 193, S. 1134-1142

U.S. EPA (2013): Integrated Science Assessment for Ozone and Related Photochemical Oxidants. U.S. Environmental Protection Agency (U.S. EPA), Washington, https://www.epa.gov/isa/integrated-science-assessment-isa-ozone-and-related-photochemical-oxidants

U.S. EPA (2020): Integrated Science Assessment (ISA) for Ozone and Related Photochemical Oxidants (Final Report). U.S. Environmental Protection Agency (U.S. EPA), Washington, https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=348522

UBA (2018): Leistungsbeschreibung. ReFoPlan 2018. Thema: "Quantifizierung der Krankehtislast verursacht durch Ozon-Exposition in Deutschland für die Jahre 2007-2016". Umweltbundesamt (UBA), Dessau-Roßlau, https://www.evergabe-online.de/

UBA (2019a): Gesundheitsrisiken der Bevölkerung durch Feinstaub. Umweltbundesamt (UBA), Dessau-Roßlau, https://www.umweltbundesamt.de/daten/umwelt-gesundheit/gesundheitsrisiken-der-bevoelkerung-durch-feinstaub#textpart-1

UBA (2019b): Ozon-Belastung. Umweltbundesamt (UBA, Dessau-Roßlau, https://www.umweltbundesamt.de/daten/luft/ozon-belastung#textpart-8

UBA (2019c): Stickstoffdioxid-Belastung. Umweltbundesamt (UBA), Dessau-Roßlau, https://www.umweltbundesamt.de/daten/luft/stickstoffdioxid-belastung

Uh, S.T., Koo, S.M., Jang, A.S., Park, S.W., Choi, J.S., Kim, Y.H., Park, C.S. (2015): Proteomic differences with and without ozone-exposure in a smoking-induced emphysema lung model. In: Korean J Intern Med, 2015, 30, S. 62-72

Vanos, J.K., Hebbern, C., Cakmak, S. (2014): Risk assessment for cardiovascular and respiratory mortality due to air pollution and synoptic meteorology in 10 Canadian cities. In: Environ Pollut, 2014, 185, S. 322-332

Vawda, S., Mansour, R., Takeda, A., Funnell, P., Kerry, S., Mudway, I., Jamaludin, J., Shaheen, S., Griffiths, C., Walton, R. (2014): Associations between inflammatory and immune response genes and adverse respiratory outcomes following exposure to outdoor air pollution: a HuGE systematic review. In: Am J Epidemiol, 2014, 179, S. 432-442

Vella, R.E., Pillon, N.J., Zarrouki, B., Croze, M.L., Koppe, L., Guichardant, M., Pesenti, S., Chauvin, M.A., Rieusset, J., Geloen, A., Soulage, C.O. (2015): Ozone Exposure Triggers Insulin Resistance Through Muscle c-Jun N-Terminal Kinase Activation. In: Diabetes, 2015, 64, S. 1011-1024

Veroniki, A.A., Jackson, D., Bender, R., Kuss, O., Langan, D., Higgins, J.P.T., Knapp, G., Salanti, G. (2019): Methods to calculate uncertainty in the estimated overall effect size from a random-effects meta-analysis. In: Res Synth Methods, 2019, 10, S. 23-43

Vinikoor-Imler, L.C., Owens, E.O., Nichols, J.L., Ross, M., Brown, J.S., Sacks, J.D. (2014): Evaluating potential response-modifying factors for associations between ozone and health outcomes: a weight-of-evidence approach. In: Environ Health Perspect, 2014, 122, S. 1166-1176

Vrijheid, M., Martinez, D., Manzanares, S., Dadvand, P., Schembari, A., Rankin, J., Nieuwenhuijsen, M. (2011): Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis. In: Environ Health Perspect, 2011, 119, S. 598-606

Wang, Y., Jia, M., Yan, X., Cao, L., Barnes, P.J., Adcock, I.M., Huang, M., Yao, X. (2017): Increased neutrophil gelatinase-associated lipocalin (NGAL) promotes airway remodelling in chronic obstructive pulmonary disease. In: Clin Sci (Lond), 2017, 131, S. 1147-1159

Weichenthal, S., Pinault, L.L., Burnett, R.T. (2017): Impact of Oxidant Gases on the Relationship between Outdoor Fine Particulate Air Pollution and Nonaccidental, Cardiovascular, and Respiratory Mortality. In: Sci Reps, 2017, 7, S. 16401

Wengler, A., Rommel, A., Plaß, D., Gruhl, H., Leddin, J., Porst, M., Anton, A., von der Lippe, E. (2019): ICD-Codierung von Todesursachen: Herausforderungen bei der Berechnung der Krankheitslast in Deutschland. In: Bundesgesundheitsbl, 2019, 62, S. 1485-1492

Werthamer, S., Schwarz, L.H., Soskind, L. (1970): Bronchial epithelial alterations and pulmonary neoplasia induced by ozone. In: Pathol Microbiol, 1970, 35, S. 224-230

WHO (2005): WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide. World Health Organization (WHO), Geneva, https://apps.who.int/iris/bitstream/handle/10665/69477/WHO_SDE_PHE_OEH_06.02_eng.pdf;jsessionid=A2A0C88667808827F985026316C09FD1?sequence=1

WHO (2006): WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide. Global update 2005. Summary of risk assessment. World Health Organitation (WHO), Geneva, https://apps.who.int/iris/bitstream/handle/10665/69477/WHO_SDE_PHE_OEH_06.02_eng.pdf?sequence=1

WHO (2013a): Health risks of air pollution in Europe – HRAPIE project Recommendations for concentration–response functions for cost–benefit analysis of particulate matter, ozone and nitrogen dioxide. World Health Organization (WHO), Copenhagen, http://www.euro.who.int/__data/assets/pdf_file/0017/234026/e96933.pdf?ua=1

WHO (2013b): Review of evidence on health aspects of air pollution - REVIHAAP Project. World Health Organization (WHO), Copenhagen, http://www.euro.who.int/__data/assets/pdf_file/0004/193108/REVIHAAP-Final-technical-report.pdf

WHO (2016): Ambient air pollution: a global assessment of exposure and burden of disease. World Health Organization (WHO), Geneva, https://www.who.int/phe/publications/air-pollution-global-assessment/en/

WHO (2020): Frequently asked questions on estimations of attributable burden of disease due to a risk factor. World Health Organization (WHO), Geneva, https://www.who.int/quantifying_ehimpacts/faqs/en/#7

Wiegman, C.H., Li, F., Clarke, C.J., Jazrawi, E., Kirkham, P., Barnes, P.J., Adcock, I.M., Chung, K.F. (2014): A comprehensive analysis of oxidative stress in the ozone-induced lung inflammation mouse model. In: Clin Sci (Lond), 2014, 126, S. 425-440

Wiegman, C.H., Michaeloudes, C., Haji, G., Narang, P., Clarke, C.J., Russell, K.E., Bao, W., Pavlidis, S., Barnes, P.J., Kanerva, J., Bittner, A., Rao, N., Murphy, M.P., Kirkham, P.A., Chung, K.F., Adcock, I.M. (2015): Oxidative stress-induced mitochondrial dysfunction drives inflammation and airway smooth muscle remodeling in patients with chronic obstructive pulmonary disease. In: J Allergy Clin Immunol, 2015, 136, S. 769-780

Williams, A.S., Eynott, P.R., Leung, S.Y., Nath, P., Jupp, R., De Sanctis, G.T., Resnick, R., Adcock, I.M., Chung, K.F. (2009): Role of cathepsin S in ozone-induced airway hyperresponsiveness and inflammation. In: Pulm Pharmacol Ther, 2009, 22, S. 27-32

Wolffe, T.A.M., Whaley, P., Halsall, C., Rooney, A.A., Walker, V.R. (2019): Systematic evidence maps as a novel tool to support evidence-based decision-making in chemicals policy and risk management. In: Environ Int, 2019, 130, S. 104871

Wong, T.W., Lau, T.S., Yu, T.S., Neller, A., Wong, S.L., Tam, W., Pang, S.W. (1999): Air pollution and hospital admissions for respiratory and cardiovascular diseases in Hong Kong. In: Occup Environ Med, 1999, 56, S. 679-683

Yan, M., Liu, Z., Liu, X., Duan, H., Li, T. (2013): Meta-analysis of the Chinese studies of the association between ambient ozone and mortality. In: Chemosphere, 2013, 93, S. 899-905

Yang, B.Y., Qian, Z., Howard, S.W., Vaughn, M.G., Fan, S.J., Liu, K.K., Dong, G.H. (2018): Global association between ambient air pollution and blood pressure: A systematic review and meta-analysis. In: Environ Pollut, 2018, 235, S. 576-588

Yang, H., Li, S., Sun, L., Zhang, X., Cao, Z., Xu, C., Cao, X., Cheng, Y., Yan, T., Liu, T., Wang, Y. (2019): Smog and risk of overall and type-specific cardiovascular diseases: A pooled analysis of 53 cohort studies with 21.09 million participants. In: Environ Res, 2019, 172, S. 375-383

Yang, H.J., Liu, X., Qu, C., Shi, S.B., Liang, J.J., Yang, B. (2017): Main air pollutants and ventricular arrhythmias in patients with implantable cardioverter-defibrillators: A systematic review and meta-analysis. In: Chronic Dis Transl Med, 2017, 3, S. 242-251

Yang, W.S., Wang, X., Deng, Q., Fan, W.Y., Wang, W.Y. (2014): An evidence-based appraisal of global association between air pollution and risk of stroke. In: Int J Cardiol, 2014, 175, S. 307-313

Yang, W.S., Zhao, H., Wang, X., Deng, Q., Fan, W.Y., Wang, L. (2016): An evidence-based assessment for the association between long-term exposure to outdoor air pollution and the risk of lung cancer. In: Eur J Cancer Prev, 2016, 25, S. 163-172

Ying, Z., Allen, K., Zhong, J., Chen, M., Williams, K.M., Wagner, J.G., Lewandowski, R., Sun, Q., Rajagopalan, S., Harkema, J.R. (2016): Subacute inhalation exposure to ozone induces systemic inflammation but not insulin resistance in a diabetic mouse model. In: Inhal Toxicol, 2016, 28, S. 155-163

Yonchuk, J.G., Foley, J.P., Bolognese, B.J., Logan, G., Wixted, W.E., Kou, J.P., Chalupowicz, D.G., Feldser, H.G., Sanchez, Y., Nie, H., Callahan, J.F., Kerns, J.K., Podolin, P.L. (2017): Characterization of the Potent, Selective Nrf2 Activator, 3-(Pyridin-3-Ylsulfonyl)-5-(Trifluoromethyl)-2H-Chromen-2-One, in Cellular and In Vivo Models of Pulmonary Oxidative Stress. In: J Pharmacol Exp Ther, 2017, 363, S. 114-125

Yoon, H.K., Cho, H.Y., Kleeberger, S.R. (2007): Protective role of matrix metalloproteinase-9 in ozone-induced airway inflammation. In: Environ Health Perspect, 2007, 115, S. 1557-1563

Yoon, S.J., Oh, I.H., Seo, H.Y., Kim, E.J. (2014): Measuring the burden of disease due to climate change and developing a forecast model in South Korea. In: Public Health, 2014, 128, S. 725-733

Zanobetti, A., Schwartz, J. (2008): Mortality displacement in the association of ozone with mortality: an analysis of 48 cities in the United States. In: Am J Respir Crit Care Med, 2008, 177, S. 184-189

Zeng, Y., Lin, R., Liu, L., Liu, Y., Li, Y. (2019): Ambient air pollution exposure and risk of depression: A systematic review and meta-analysis of observational studies. In: Psychiatry Res, 2019, 276, S. 69-78

Zhang, J.J., Wei, Y., Fang, Z. (2019): Ozone Pollution: A Major Health Hazard Worldwide. In: Front Immunol, 2019, 10, S. 2518

Zhang, R., Lei, W., Tie, X., Hess, P. (2004): Industrial emissions cause extreme urban ozone diurnal variability. In: Proc Natl Acad Sci U S A, 2004, 101, S. 6346-6350

Zhang, M., Fei, X., Zhang, G.Q., Zhang, P.Y., Li, F., Bao, W.P., Zhang, Y.Y., Zhou, X. (2016a): Role of neutralizing anti-murine interleukin-17A monoclonal antibody on chronic ozone-induced airway inflammation in mice. In: Biomed Pharmacother, 2016a, 83, S. 247-256

Zhang, S., Li, G., Tian, L., Guo, Q., Pan, X. (2016b): Short-term exposure to air pollution and morbidity of COPD and asthma in East Asian area: A systematic review and meta-analysis. In: Environ Res, 2016b, 148, S. 15-23

Zhang, X., Bao, W., Fei, X., Zhang, Y., Zhang, G., Zhou, X., Zhang, M. (2018): Progesterone attenuates airway remodeling and glucocorticoid resistance in a murine model of exposing to ozone. In: Mol Immunol, 2018, 96, S. 69-77

Zhao, L., Liang, H.R., Chen, F.Y., Chen, Z., Guan, W.J., Li, J.H. (2017a): Association between air pollution and cardiovascular mortality in China: a systematic review and meta-analysis. In: Oncotarget, 2017a, 8, S. 66438-66448

Zhao, R., Chen, S., Wang, W., Huang, J., Wang, K., Liu, L., Wei, S. (2017b): The impact of short-term exposure to air pollutants on the onset of out-of-hospital cardiac arrest: A systematic review and meta-analysis. In: Int J Cardiol, 2017b, 226, S. 110-117

Zhao, T., Markevych, I., Janßen, C., Nowak, D., Steckling-Muschack, N., Heinrich, J. (2020): Ozone exposure and health effects: a protocol for an umbrella review and effect-specific systematic maps. In: BMJ open, 2020, 10, S. e034854

Zhao, T., Markevych, I., Nowak, D., Heinrich, J., Steckling-Muschack, N. (2019): Ambient ozone exposure and health effects: a systematic review of epidemiological studies. In: PROSPERO, 2019, 23/04/2019; Zugang am 12.10.2020 unter https://www.crd.york.ac.uk/prospero) unter der Registrierungsnummer CRD42019123064

Zhao, T., Markevych, I., Romanos, M., Nowak, D., Heinrich, J. (2018): Ambient ozone exposure and mental health: A systematic review of epidemiological studies. In: Environ Res, 2018, 165, S. 459-472

Zheng, X.Y., Ding, H., Jiang, L.N., Chen, S.W., Zheng, J.P., Qiu, M., Zhou, Y.X., Chen, Q., Guan, W.J. (2015): Association between Air Pollutants and Asthma Emergency Room Visits and Hospital Admissions in Time Series Studies: A Systematic Review and Meta-Analysis. In: PloS one, 2015, 10, S. e0138146

Zhong, J., Allen, K., Rao, X., Ying, Z., Braunstein, Z., Kankanala, S.R., Xia, C., Wang, X., Bramble, L.A., Wagner, J.G., Lewandowski, R., Sun, Q., Harkema, J.R., Rajagopalan, S. (2016): Repeated ozone exposure exacerbates insulin resistance and activates innate immune response in genetically susceptible mice. In: Inhal Toxicol, 2016, 28, S. 383-392

Zychowski, K.E., Lucas, S.N., Sanchez, B., Herbert, G., Campen, M.J. (2016): Hypoxia-induced pulmonary arterial hypertension augments lung injury and airway reactivity caused by ozone exposure. In: Toxicol Appl Pharmacol, 2016, 305, S. 40-45

7 Anhang

A Beschreibung der identifizierten systematischen Reviews zu Ozon und Gesundheit (mit Metaanalysen), geordnet nach den Gesundheitsendpunkten und Publikationsjahr (Umbrella Review)

Health endpoint	**Study**	**Population**	**Expo-sure**	**Compa-rison**	**Outcome**	**Time frames for search**	**Papers in systematic review, ozone (overall)**	**Major study type**	**Result from systematic review**	**Measure of effect**	**Point estimate and 95 % CI**
Mortality and hospital admissions	Stieb et al. 2002	All, international	Short	Na	Mortality	Last updated in December 2000	109	109 time-series	“PM$_{10}$, CO, NO$_2$, O$_3$, and SO$_2$ were all positively and significantly associated with all-cause mortality.”	Percent excess mortality	Overall, single-pollutant effect, 1.6 (1.1, 2.0); overall, multipollutant models, 0.6 (0.2, 1.4); respiratory, 1.7 (-0.7, 4.1); circulatory, 2.1 (0.7, 3.5); elderly, 1.6 (1.1, 2.6); cool season, 0.4 (-1.2, 2.6); warm season, 1.9 (0.7, 3.1);
	Bell et al. 2005	All, international	Short	Na	Mortality	From 1990 to 21 June 2004	39	Time-series	Larger effects for cardiovascular mortality than for total mortality; larger effects at lag 0 as compared with lags 1 or 2; and a lack of confounding by PM.	Posterior Means	Total, 0.87 (0.55, 1.18); cardiovascular diseases, 1.11 (0.68, 1.53); respiratory, 0.47 (-0.51, 1.47);
	Smith et al. 2009	All, international	Short	Na	Mortality	Up to May 2009	22	22 time-series	“Time-series studies of daily mortality have consistently noted associations with ozone in Europe, the USA, and Canada. Our systematic review and meta-analysis of short-term exposure time-series studies of black smoke (and ozone) and daily mortality detected significant, positive associations with all-cause, cardiovascular, and respiratory mortality. “	Percentage change	All-cause single-city estimates, 0.03 (0.02, 0.04); cardiovascular single-city estimates, 0.04 (-0.03, 0.05); respiratory single-city estimates, 0.04 (0.01, 0.0 7);

Health endpoint	Study	Population	Expo-sure	Compa-rison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Ji et al. 2011	All, international	Short	Na	Respiratory hospital admissions	1990 to 2008	93	Time-series or case-crossover	“Observed associations between ozone and hospitalization or emergency visits for all disease categories: total or general respiratory disease, pneumonia, COPD or asthma.”	Percentage change	Respiratory disease (RD) General hospital admissions Total RD (all ages), 2.03 (-0.21, 4.31) Total RD (elderly), 2.47 (0.89, 4.04) Total RD (children), 0.69 (-2.03, 3.48) Pneumonia (elderly), 4.24 (2.85, 5.63) COPD (all ages), 5.74 (0.71, 10.96) COPD (elderly), 2.54 (1.29, 3.80) Asthma (all ages), 4.35 (-0.18, 9.10) Asthma (children), -0.68 (-6.56, 5.57) Emergency hospital admissions Total RD (all ages), 1.90 (0.74, 3.07) Total RD (elderly), 4.47 (2.48, 6.50) Total RD (15-64 years), 1.06 (-1.31, 3.47) COPD (all ages), 5.06 (1.24, 9.05) Asthma (all ages), 6.64 (2.60, 10.85) Asthma (children), 2.83 (-3.45, 9.52) Asthma (15-64 years), 3.63 (-2.02, 9.60) Emergency visits Total RD (all ages), 1.23 (0.29, 12.17) Total RD (children), 2.55 (-1.71, 6.98) Asthma (all ages), 4.50 (2.05, 6.99) Asthma (children), 3.67 (1.55, 5.81)
	Atkinson et al. 2012	All, Asian	Short	Na	Daily mortality, hospital admissions	1980 - Sep 2007	52 (82)	52 time series	“Random effects estimate for all-cause mortality was 0.07 % (95 % CI, -0.16 %, 0.30 %) per 10 µg/m^3 increase in 8 hr ozone.”		Mortality all-8h, 0.07 (-0.016, 0.30) all-24h, 0.07 (-0.07, 0.21) **Respiratory, 0.073 (0.30, 1.16)** cardiovascular, 0.16 (-0.11, 0.44) Admissions Respiratory, 0.26 (-0.06, 0.59)

Health endpoint	Study	Population	Expo-sure	Compa-rison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Lai et al. 2013	All, Chinese	Short and long	Na	Health outcomes were related to deaths, births and hospital utilization	To Jun 30, 2012	22 (48)	Na	"Evidence on short-term effects of air pollution is consistent and sufficient for health impact assessment but that on long-term effects is still insufficient."	RR or percentage change	Short term Mortality **all-cause, 1.0042 (1.0030, 1.0054)** **cardiovascular diseases, 1.0051 (1.0026, 1.0076)** **respiratory diseases, 1.0048 (1.0021, 1.0075)** cardiopulmonary diseases, 1.0023 (0.9993, 1.0052) cardiac diseases, 1.0026 (0.9965, 1.0087) **cerebrovascular diseases, 1.0057 (1.0000, 1.0147)** COPD, 1.0071 (0.9994, 1.0044) **non-cardiopulmonary, 1.0025 (1.0005, 1.0120)** accidental, 1.0005 (0.9889, 1.0120) Morbidity hospital admissions cerebrovascular diseases, 0.9994, (0.9957, 1.0031) ischemia heart diseases, 1.0024 (0.9983, 1.0065)
	Shang et al. 2013	All, Chinese	Short	Na	Daily mortality, total mortality; respiratory mortality; cardiovascular mortality	January 1990 and July 2012	26 (33) 8 total mortality; 9 respiratory mortality; 9 cardiovascular mortality	8 time-series and case-crossover	Combined estimates in the meta-analysis showed that exposures to O_3 are significantly associated with increased all-cause and cardio-respiratory mortality risks in Chinese population.	ER, excess risk;	Total mortality, 0.48 % (0.38, 0.58); respiratory mortality, 0.73 % (0.49, 0.97); cardiovascular mortality, 0.45 % (0.29, 0.60)
	Yan et al. 2013	All, Chinese	Short	Na	Mortality	1990 -	5	5 time-series	A small but substantial association between ambient ozone level and mortality was observed in Mainland China.	Percentage change	Non-accident mortality 0.42 (0.32, 0.52) cardiovascular mortality 0.44 (0.17, 0.70) respiratory mortality 0.50 (0.22, 0.77)

Health endpoint	Study	Population	Expo-sure	Compa-rison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Atkinson et al. 2016	All, international	Long	Na	Mortality: (all causes, cardiovascular, respiratory, ischemic heart disease, lung cancer)	1974 to week 40, 2015; 1946 to September week 4, 2015; to 6 Oct, 2015	14(14)	Cohort	Revealed a paucity of independent studies regarding the associations between long-term exposure to ozone and mortality.	HR	All year: all causes 0.96 (0.92, 1.00) cardiovascular 0.98 (0.93, 1.04) ischemic heart disease 1.00 (0.92, 1.09) cardiopulmonary 0.98 (0.90, 1.07) respiratory 0.94 (0.81, 1.10) lung cancer 0.95 (0.98, 1.08) warm season all causes 1.00 (0.99, 1.02) cardiovascular 1.01 (1.00, 1.02) respiratory 1.03 (1.01, 1.05)
	Requia et al. 2018	All, international	Short	Na	Cardiorespiratory disease (hospital admissions and mortality) Respiratory diseases: ICD-9 460-519 or ICD-10 J00-J98; Cardiovascular diseases: ICD-9 390-459 or ICD-10 I00-I99	2006 to May 11, 2016	7 (70)	Time serious	With regard to hospital admissions, the youngest age group (aged < 5 years) demonstrated the highest risk. Respiratory diseases showed the strongest association, for ozone, the found risk equaled to 2.4 % (95 % CI: 1.6 %, 3.7 %). For mortality, the youngest age group demonstrated the highest risk for ozone. Respiratory diseases showed the highest risk for ozone (0.8 %, 95 % CI: 0.2 %, 2.3 %).	Percentage risk	Hospital admissions Respiratory, 2.4 % (1.6, 3.7) Mortality Respiratory, 0.8 % (0.2, 2.3)

Health endpoint	Study	Population	Expo-sure	Compa-rison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Yang et al. 2019	All, international	Long (in Discussion)	Na	Stroke, ischemic heart disease, heart failure, coronary heart disease, myocardial infarction, and overall CVD events (mortality, morbidity, or both)	From the inception to April 25, 2018	8 (35)	8 cohort	O_3 exposure was separately associated with an increased risk of CVD mortality.	RR	CVD mortality 1.03 (1.02, 1.05); CVD events 0.93 (0.81, 1.04); stroke events 0.93 (0.76, 1.10); stroke incidence 0.81 (0.40, 1.22); stroke mortality 1.02 (1.00, 1.05); IHD mortality 1.04 (1.00, 1.09)

Health endpoint	**Study**	**Population**	**Expo-sure**	**Compa-rison**	**Outcome**	**Time frames for search**	**Papers in systematic review, ozone (overall)**	**Major study type**	**Result from systematic review**	**Measure of effect**	**Point estimate and 95 % CI**
Respiratory health effects	Zheng et al. 2015	All, international	Short	Na	Asthma exacerbations (hospital admission and ER visit).	Up to March 2015	71 (87)	62 time-series; 25 case-crossover	"Air pollutants were associated with significantly increased risks of asthma ervs and hospitalizations. … Sensitivity analyses yielded compatible findings as compared with the overall analyses without publication bias. Stronger associations were found in hospitalized males, children and elderly patients in warm seasons with lag of 2 days or greater."	RR	Overall, 1.009 (1.006, 1.0011); study quality sensitivity analyses, 1.005 (1.002, 1.008); lag exposure sensitivity analyses, 1.010 (1.005, 1.014) Sex males,1.009 (0.993, 1.025); females, 1.023 (1.006, 1.024); Age children, 1.008 (1.005, 1.012); adults, 1.013 (1.008, 1.018); elderly, 1.010 (1.002, 1.017); season cold. 1.017 (1.007, 1.028); warm, 1.016 (1.010, 1.021) type of admission ERV, 1.007 (1.004, 1.010); HA, 1.010 (1.006, 1.014); lag patter lag ⩽ 2days, 1.007 (1.004, 1.011); lag > 2 days, 1.010 (1.006, 1.013)
	Li et al. 2016a	All, international	Short	Na	Risk of COPD exacerbations	Through March 30, 2016	29 (59)	13 case-crossover, 46 time-series	"A significant association between short-term exposure to major air pollutants and COPD emergency risk, especially for O_3 and NO_2. Subgroup analysis showed lower heterogeneities and yielded similar associations in the overall analysis."	RR	Overall, 1.028 (1.011, 1.044); publication adjusted, 0.976 (0.962, 0.991); lag 0, 0.96 (0.95, 0.96); lag 1, 1.01 (1.01, 1.01); lag 2, 1.01 (1.00, 1.01); lag 3, 1.01 (1.01, 1.02)

Health endpoint	Study	Population	Expo-sure	Compa-rison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Moore et al. 2016	All, international	Short	Na	COPD exacerbation qualified by hospital admissions	Between 1980 and September 2015	23 (46)	Time-series and case-crossover	"Effects of separate pollutants on COPD admissions appear to vary across geographical regions. … Researchers in 18 of the 22 studies reported a positive effect; however, it was significant in only 10 studies. Overall, the pooled estimates showed that there was a small positive effect of O_3 on COPD hospital admissions (OR, 1.02; 95 % CI, 1.01–1.03)."	OR	Asian ,1.04 (1.03, 1.05) North America, 1.01 (1.00, 1.02) European, 1.01 (0.99, 1.04) overall, 1.02 (1.01, 1.03)
	Yang et al. 2016	All, international	Long	Na	Lung cancer	Through 31 May 2014	5 (21)	Cohort	There was a null association for carbon monoxide and ozone.	RR	0.94 (0.81, 1.08)
	Zhang et al. 2016b	All, East Asian area	Short	Na	Hospital utilization for either COPD or asthma	Up to December 2014	19 (30)	Time-series and case-crossover	Evidence was found that short-term exposure to air pollution was associated with increasing risk of hospital utilization for COPD and asthma in the whole population, the elderly and children.	RR	COPD all type, all ages 1.028 (1.016, 1.040); general hospital admissions, all ages 1.028 (1.001, 1.056); emergency hospital admissions, all ages 1.028 (1.019, 1.037); asthma all ages, 1.025 (1.018, 1.033); children, 1.029 (1.022, 1.037); adults, 1.026 (0.999, 1.055); general hospital admissions all ages, 1.026 (1.016, 1.035); children, 1.027 (1.020, 1.035); emergency hospital admissions all ages, 1.033 (1.030, 1.037); adults, 1.027 (0.999, 1.055)

Health endpoint	Study	Population	Exposure	Comparison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Hehua et al. 2017	Children, international	Long	Na	Asthma or wheeze	June 6, 2017	2 (18)	2 nested case-control based on cohort	Pooled analysis of O_3 showed no significant effect of prenatal exposure on childhood asthma occurrence.	OR or RR	1.05 (0.91, 1.21)
	Nhung et al. 2017	Children, international	Short	Na	Hospitalization due to pneumonia	Up to January 3rd, 2017	12 (17)	11 time-serious; 6 cross-over	“Positive associations between all pollutantsconsidered and pediatric hospital admissions due to pneumonia.”	Excess risk percentage (ER %)	Pneumonia hospitalization 1.7 % (0.5, 2.8)
	Orellano et al. 2017	All, international	Short	"Not applicable"	"Severe asthma exacerbations are defined as an episode of wheezing or shortness of breath that include the need for oral or systemic corticosteroids, and require hospitalization or an emergency room visit."	Between January 2000 and October 2016	11 (22)	22 case-crossover	“A significant association between the main pollutants, with the exception of SO_2 and PM_{10}, and moderate or severe exacerbations of asthma. … This meta-analysis provides evidence of the association between selected air pollutants and asthma exacerbations for different lags.”	OR	1.022 (1.000, 1.045); studies with a NOS scale ⩾ 6, 1.020 (1.013, 1.027)

Health endpoint	Study	Population	Expo-sure	Compa-rison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Luong et al. 2019	Children, southeast Asia area	Short	Na	Outcome measure related to wheeze associated disorders such as hospital admission, emergency room visit, prevalence, incidence, mortality for any symptom of wheeze associated disorders.	On 24 July 2018	4 (10)	4 time-series; 1 panel; 1 cohort; 3 cross-sectional; 1 case-crossover	Positive associations were found for PM_{10}, but not for CO and O_3, SO_2, NO_2, NO_x.	RR	0.999 (0.998, 1.001)
Neurological health effects	Yang et al. 2014	All, international	Short	Na	Risk of stroke hospitalization and mortality	From their inception to October 2013	20 (34)	20 time-series; 14 case cross-over	An increased risk of stroke hospitalizations and mortality with a transient increase in major ambient air pollutants ($PM_{2.5}$, PM_{10}, SO_2, CO, and NO_2). We also found a positive association between exposure to ozone and ischemic stroke.	RR (percent increase in Tables)	Overall, 1.0048 (-0.9996, 1.0101) ischemic stroke, 1.0245 (1.0035, 1.0460)

Health endpoint	**Study**	**Population**	**Exposure**	**Comparison**	**Outcome**	**Time frames for search**	**Papers in systematic review, ozone (overall)**	**Major study type**	**Result from systematic review**	**Measure of effect**	**Point estimate and 95 % CI**
	Shah et al. 2015a	All, international	Short	"Not relevant."	"Stroke admission. Stroke mortality." admission to hospital for stroke or mortality from stroke	To Jan 21, 2014	53(94)	56 time-serious 40 case-crossover	"A positive association between all gaseous and particulate air pollutants and admission to hospital for stroke or mortality from stroke, with the weakest association seen for ozone."	RR	Overall 1.001 (1.000, 1.002) Admisssion 1.001 (1.000, 1.002) Mortality 1.004 (1.001, 1.006)
	Hu et al. 2019	All, international	Long	Na	Parkinson's disease	Inceptions to October 1, 2017	3 (10)	3 case-control	O_3 exposure were associated with an increased risk of PD, although there is high risk of bias.	RR	1.01 (1.00, 1.02)
	Kasdagli et al. 2019	All, international	Long, and short (not for ozone)	Na	Parkinson's disease	Until 7th November 2018	5 (15)	7 case-control; 8 cohort	There were indications of associations with long-term exposures to $PM_{2.5}$, CO, NO_2 and O_3 among which only the last one reached the nominal level of significance.	RR	Per 5 ppb, 1.01 (1.00, 1.02); high vs low exposure, 1.01 (0.81, 1.26)
Cardiovascular and vascular health effects	Mustafic et al. 2012	Adults, international	Short, defined as an exposure of up to 7 days	Na	Myocardial infarction (MI), heart attack, acute coronary syndrome	Between 1948 and November 28, 2011	19 (34)	(overall) 17 time-series; 17 case-crossover	"All the main air pollutants, with the exception of ozone, were significantly associated with an increase in MI risk." For ozone, the RR was 1.003 (95 % CI, 0.997-1.010; P=.36). "Subgroup analyses provided results comparable with those of the overall analyses."	RR	Overall, 1.003 (0.997, 1.010); study quality subgroup, 0.998 (0.994, 1.002); lag exposure subgroup, lag0, 0.992 (0.982, 1.002)

Health endpoint	Study	Population	Exposure	Comparison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Shah et al. 2013	All, international	Short	Na	Heart failure hospitalization or heart failure mortality	Between 1948 and July 15, 2012	18 (35)	10 case-crossover; 24 time-series; 1 both	"There was a positive association between heart failure hospitalization or heart failure mortality, and all gaseous and particulate air pollutants except ozone. The strongest associations were seen at lag 0, with this effect diminishing at longer lag times."	Percentage risk	Overall, 0.46 (-0.10, 1.02); lag 0, -0.07 (-0.35, 0.22); lag 1, 0.89 (-0.41, 2.21); non-adjusted, RR, 1.005 (0.999, 1.011); publication bias adjusted, RR, 1.001 (0.995, 1.007)
	Cai et al. 2016	All, international	Long and short	Na	Hypertension	Published before September 1, 2015	2 (17)	2 short-term case-crossover; 1 long-term cross-sectional	O_3 had positive relationships with hypertension, but lacked statistical significance "Short-term exposure to SO_2, $PM_{2.5}$, and PM_{10} and long-term exposure to NO_2 and PM_{10} were associated with an increase in hypertension risk."		

Health endpoint	Study	Population	Expo-sure	Compa-rison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Li et al. 2017a	All, international	Short	Na	Non-accidental and cardiovascular mortality	Up to 2nd December 2014	10 (21)	Time-series and case-crossover	A statistically significant interactive effect between temperature and levels of PM_{10} and O_3 acting on both non-accidental and cardiovascular mortality. Extreme high temperature significantly increased the effect of PM10 and O_3 on non-accidental and cardiovascular mortality, whereas the effect of PM_{10} on cardiovascular mortality was decreased during low temperature days. Our meta-analysis also found a significant synergistic effect between low temperature and O_3 acting on non-accidental mortality. We did not observe an interaction between SO_2 and NO_2 with either high or low temperature and this may be due to the small number of studies on these pollutants.	Percentage change	Non-accidental low, 0.48 (0.28, 0.69); normal, 0.20 (0.07, 0.34); high, 0.47 (0.32, 0.63); high (trim and fill method), 0.50 (0.30, 0.60); cardiovascular low, 0.59 (0.27, 0.92); normal, 0.27 (0.03, 0.51); high, 1.63 (1.14, 1.21); non-accidental, Asia low, 1.39 (0.90, 1.88); normal, 0.13 (-0.39, 0.65); high, 0.42 (-0.34, 1.18); non-add dental, combine the multi-city and single city results low, 0.48 (0.28, 0.69); normal, 0.20 (0.09, 0.32); high, 0.49 (0.35, 0.64); high (trim and fill method), 0.49 (0.35, 0.64); cardiovascular, Asia low, 0.56 (0.89, 2.03); normal, 0.20 (-1.10, 1.51); high, 0.56 (-0.89, 2.03); cardiovascular, combine the multi-city and single city results low, 0.59 (0.27, 0.92); normal, 0.22 (0.02, 0.42); high, 1.62 (1.14, 2.10)
	Shao et al. 2016	All, international	Short	Na	Atrial fibrillation	Before March 2015	4 (4)	4 case-crossover	Changes in gaseous and particulate air pollutant concentrations have a close association with new onset AF.	Population-attributable risk	1.09 (0.20, 1.86)

Health endpoint	Study	Population	Exposure	Comparison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Song et al. 2016	All, international	Short	"We plan to include case-crossover and time-series studies. The two techniques have their own characteristics, and the comparators will differ accordingly." (Protocol)	"Change in hospitalization or mortality associated with arrhythmia when air pollution increases above standard levels." (Protocol)	From inception to 20 June 2015	10 (25)	(overall) 11 case-crossover; 13 time-series; 1 both	Both particulate and gaseous components, with the exception of ozone, have a temporal association with arrhythmia hospitalization or mortality. The strongest associations were observed at the same day of exposure across all pollutants. In addition, a stronger association was noted in Asia.	RR	Overall, 1.012 (0.997, 1.027); age, all, 1.019 (0.999, 1.039); age, ⩾ 65, 0.993 (0.969, 1.017); outcome, hospitalization, 1.016 (0.997, 1.035); outcome, mortality, 0.997 (0.975, 1.018); study design, case-crossover, 1.037 (0.996, 1.078); study design, time-series, 1.003 (0.996, 1.010); location, Europe, 1.002 (0.991, 1.014); location, North America, 0.998 (0.989, 1.008); location, asia, 1.086 (1.033, 1.141)

Health endpoint	Study	Population	Expo-sure	Compa-rison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Tang et al. 2016	All, international	Long and short	"Participants in case-cross over design and time-series design are self-controlled. In cohort study design, control referred to participants experienced low levels (<10th) of these air pollutants." CO, NO_2, SO_2, O_3, PM	"Hospital admissions for venous thrombosis"	Na	2 (8)	2 time-series; 3 case-crossover; 2 prospective cohort; 1 case-control	No significant association was observed between the three air pollutants ($PM_{2.5}$, PM_{10}, NO_2) and venous thrombosis.	Meta-analysis not for ozone exposure	
	Zhao et al. 2017b	All, international	Short	Na	Out-of-hospital cardiac arrest (OHCA)	Up to July 1st, 2016	11 (15)	11 case-crossover; 2 time-series; 2 both	Short-term exposure to PM_{10}, $PM_{2.5}$ and O_3 was associated with the incidence of OHCA, with the strongest association being between OHCA risk and $PM_{2.5}$. The strongest estimated effect was all observed at lag01 for PM_{10}, $PM_{2.5}$ and O_3.	RR	Overall, 1.02 (1.01, 1.02); publication bias adjusted, 1.01 (1.00, 1.02)

Health endpoint	Study	Population	Expo-sure	Compa-rison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Zhao et al. 2017a	All, not from specific high-risk groups (e.g. Smokers or children), Chinese	Short	Na	Cardiovascular mortality	Up to January 2017,	(8 in Table 1/systematic review?) 6 (30)	2 case-crossover; 28time-series	Short-term exposure of air pollution is associated with greater cardiovascular mortality. Strongest associations “were seen for lag 0–1 day of exposure among all pollutants. Female, lower temperature, and age > 65 years were associated with greater risks of cardiovascular mortality for all pollutants.”	Excess risk (ER) percentages	Overall, 0.62 (0.33, 0.92); lag 2, 0.40 (-0.04, 0.84); lag 0-1, 1.15 (-1.32, 4.33); warm season, 0.43 (0.15, 0.71); cool season, 1.72 (-0.71, 4.15)
	Yang et al. 2017	All, international	Short	Na	Risk of ventricular arrhythmias in the patients with implantable cardioverter-defibrillator	1948 to June 31, 2017	6 (7)	5 case-crossover 1 time-series	No increased risk of ventricular arrhythmias in the patients with implantable cardioverter-defibrillator was found to be associated with O_3.	OR	Ventricular arrhythmia in the patients with implantable cardioverter-defibrillator 1.00 (0.98, 1.01)

Health endpoint	Study	Population	Expo-sure	Compa-rison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Newell et al. 2018	Adults, low and middle income countries (lmics), as defined by the World Bank Classification	Short	Na	Cardiorespiratory health effects	Up until the 28th November 2016	16 (60) mortality 10; morbidity 5	16 time-series	“Acute exposure to gaseous ambient air pollution (AP) is associated with increases in morbidity and mortality” in low and middle income countries (lmics), with greatest associations observed for cardiorespiratory mortality. Further research is required within lmics exclusively to fully examine the health effects of gaseous AP. “Our results for O_3 were however similar regarding cardiovascular mortality to those observed in High income country (hics).”	Excess risk	Mortality, same day, not significant mortality, lag 0-1, 0.39 (0.07, 0.71) mortality, lag 0-3, not significant cardiovascular mortality lag 0, 0.10 (-0.17, 0.37) lag 0-1, 0.39 (0.07, 0.71) lag 0-3, 0.32 (-0.06, 0.69) lag 1-2, 0.67 (0.23, 1.11) respiratory mortality lag 0, 0.36 (-0.16, 0.88) lag 0-1, 0.26 (-0.09, 0.61) lag 0-3, 0.19 (0.08, 0.31)

Health endpoint	Study	Population	Expo-sure	Compa-rison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Yang et al. 2018	All, international	Long and short	Na	The definition of hypertension included systolic blood pressure (SBP) >=140mm Hg or diastolic blood pressure (DBP) >=90 mm Hg, self-reportedly taking antihypertensive medicine, self-report of doctor-diagnosed hypertension, or categorized by the International Classification of Disease (10th revision for hypertension, ICD10: I10 or ICD9: 401	Before 25 May 2017	Long-term exposure 4, SBP; 4, DBP; short-term exposure 4, hypertension; 5, SBP; 5, DBP	1 cohort; 8 cross-sectional; 2 case-crossover; 3 panel	A positive association of exposure to ambient air pollutants with increased arterial BP and established hypertension.	OR; beta value	Long-term exposure SBP, 0.65 (-0.19, 1.48); DBP, 0.17 (-0.02, 0.36); short-term exposure hypertension, 1.05 (0.98, 1.12); SBP, 0.06 (-0.25, 0.36); DBP, 0.13 (-0.01, 0.28)

Health endpoint	Study	Population	Exposure	Comparison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
Reproductive health effects	Hu et al. 2014	Females, pregnant women, international	Long	Na	Hypertensive disorders of pregnancy (gestational hypertension, preeclampsia and eclampsia)	Jan 1, 1980 to Sep, 2013	5(10)	4 cohort 1 case-control	Significant associations between HDP and ozone (OR per 10 ppb = 1.09, 95 % CI: 1.05, 1-13)	OR	HDP (gestational hypertension and preeclampsia), Trimester 1, 1.09 (1.05, 1.13) Trimester 2, 1.12 (0.90, 1.39)
	Pedersen et al. 2014	Females, international	Long	Na	Pregnancy-induced hypertensive disorders (i.e., gestational hypertension and preeclampsia as separate outcomes or a combination of these conditions)	Between December 2009 and December 19, 2013.	5 (17)	16 cohort; 1 case-control	O_3 showed increased risks of hypertensive disorders in pregnancy Statistically significant increased risks for hypertensive pregnancy disorders in association with exposure to $PM_{2.5}$, NO_2, and PM_{10} combined. Exposure to $PM_{2.5}$ and NO_2 during pregnancy when all studies were also associated with significantly increased risk for preeclampsia.	OR	All outcomes, 1.06 (0.99, 1.14); preeclampsia, 1.09 (0.98, 1.21)
	Elshahidi 2019	Women, international	Long	Na	Gestational diabetes mellitus (GDM)	From dates of inception till Oct 2, 2017	4 (8)	8 cohort; 1 case-control	"Effect estimates of the relationship between GDM and air pollutants ranged from 0.97 (95 % CI 0.94-0.99)" for PM_{10} to 1.47 (95 % CI 0.88-2.06) for CO. However, only NO and SO_2 "showed statistically significant effect estimates. In most studies, the second trimester was the most vulnerable period."	OR	Overall, 1.05 (0.94, 1.16); 1st trimester, 1.03 (0.86, 1.20); 2nd trimester, 1.13 (0.97, 1.29); 3ed trimester, 0.98 (0.69, 1.28)

Health endpoint	Study	Population	Expo-sure	Compa-rison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
Birth outcomes	Vrijheid et al. 2011	All, international	Long	Na	Congenital anomalies	Na published between 2002 and 2011	7 (10)	7 case-control; 1 birth cohort; 1 cohort; 1 time-series	“Meta- analyses suggest that NO_2 and SO_2 exposures were related to statistically significant increases in risk of coarctation of the aorta and tetralogy of Fallot, and PM_{10} exposure to an increase in risk of asds.”	OR	Continuous exposure cardiac anomalies atrial septal defect, (asd),1.10 (0.92, 1.32); ventricular septal defect, (vsd),0.95 (0.83, 1.08); conotruncal defects, 1.07 (0.96, 1.19); orofacial clefts cleft lip/palate, 1.10 (0.99, 1.21); cleft plate, 0.99 (0.84, 1.18)
	Stieb et al. 2012	Children, international	Long	Na	Outcome of preterm birth (o37 weeks gestation)/gestational age, birth weight/low birth weight (LBW) (o2500 g)/small for gestational age (SGA)/ intrauterine growth restriction (IUGR) (o10th percentile for gestational age)	On/after January 1, 1980; updated in January 2011.	19 (62)	17 cohort; 2 case-control cohort	We observed pooled estimates of decrease in birth weight, low birth, preterm birth attributable to representative concentrations of CO, NO_2, PM_{10}, and $PM_{2.5}$. Results were less consistent for ozone.	Percentage change, OR	Change in birth weight -10.0 (-32.4, 12.4); birth weight 1.01 (0.82, 1.25); preterm birth 0.97 (0.86, 1.10)

Health endpoint	Study	Population	Exposure	Comparison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Chen et al. 2014	Females, pregnant women, international	Na, (long)	Na	Congenital anomalies	January 2011 and January 2014; articles used in the previous literature synthesis published in 2011.	17, systematic; 13 meta-analysis	12 case-control; 5 cohort, 1 both	"Compared 21 combinations of air pollutants and congenital anomalies types and only one significant result was revealed. This finding could stem from strong heterogeneity in study designs."	OR	Ventricular septal defects, 0.999 (0.963, 1.036); atrial septal defects, 1.020 (0.960, 1.084); cleft lip, 1.17 (0.98, 1.41)
	Rao et al. 2016	Children, international	Long	Na	Orofacial cleft anomalies; Cleft palate (CP), cleft lip (CL), cleft lip with or without palate (CL/P)	January 1980 to December 2012	8 (8)	7 case-control; 1 cohort	"Ozone was most consistently associated with an increased risk of orofacial cleft anomalies compared to other air pollutants. … A consistent linear or dose response relationship between any one air pollutant and orofacial cleft anomalies was generally not found among the reviewed studies."	OR	CL/P, 1.08 (1.01, 1.16); CP, 1.08 (0.95, 1.22)

Health endpoint	Study	Population	Expo-sure	Compa-rison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
	Siddika et al. 2016	Women, international	Long and short	Na	The risk of stillbirth, or reported the occurrence of stillbirth	Inception to mid-April, 2015,	2 (13)	2 short-term; 11 long-term; 6 cohort; 2 semi ecological; 2 cross-sectional	“Prenatal exposure to air pollution increases the risk of stillbirth. The summary effect estimates from the random effects models were systematically elevated, although they did not reach statistical significance. … The point estimates for the third trimester were slightly elevated for SO_2, CO, PM_{10} and O_3 consistently, with a hypothesis of a susceptible time window for the adverse effects, although the differences were not statistically significant.”	Effect estimates (EE)	Overall, 1.00 (0.971, 1.034); 1st trimester, 1.001 (0.983, 1.020); 2nd, 0.991 (0.944, 1.040); 3rd, 1.012 (0.966, 1.060)
	Guo et al. 2019	Children, newborn, international	Na long and short	"Not applicable"	Adverse birth outcomes; preterm birth (PTB), birth weight/low birth weight (LBW), small for gestational age (SGA)	From January 1980 to March 2017	4 (40)	11 case-control; 29 cohort	Pooled “ors of 1.03–1.21 for LBW and 0.97–1.06 for PTB when mothers were exposed to CO, NO_2, nox, O_3, $PM_{2.5}$, PM_{10}, and SO_2 throughout their pregnancy.”	OR	LBW, 1.06 (0.95, 1.19); PTB, 1.04 (1.00, 1.07)

Health endpoint	Study	Population	Exposure	Comparison	Outcome	Time frames for search	Papers in systematic review, ozone (overall)	Major study type	Result from systematic review	Measure of effect	Point estimate and 95 % CI
Mental health	Flores-Pajot et al. 2016	Childre, international n	Long	Na	Autism spectrum disorder (ASD), or autism	Before March 30th, 2016	2 (12)	1 cohort; 2 case-control	“O_3 exposure was weakly associated with ASD during the third trimester of pregnancy and during the entire pregnancy, however, these estimates were also based on only two studies.”	RR	During entire pregnancy, 1.05 (1.01, 1.10), during the first trimester 1.00 (0.98, 1.02), during the second trimester 1.02 (0.99, 1.04), during the third trimester 1.03 (1.02, 1.05), after birth 1.35 (0.94, 1.95)
	Zeng et al. 2019	All, international	Long and short	Na	Depression	Establishment to September 20, 2018	8 (13) meta-analysis 7 (14), systematic review	9 cohort; 3 case-crossover; 1 time-series; 3 cross-section	The authors found that air pollutants exposure was associated with increased risk of depression except for O_3.	OR	Overall, 1.01 (0.99, 1.03); depressive symptom, 0.98 (0.83, 1.16); depressive disorders, 1.00 (0.98, 1.02)
Endocrine health effects	Li et al. 2014	All, international	Long and short	"Participants not exposed to increments in gaseous (nitrogen dioxide, Sulphur dioxide, ozone, carbon monoxide) and particulate (diameter <2.5 µm [$PM_{2.5}$] or <10 µm [PM_{10}]) air pollutants. "	"Diabetes-associated mortality." diabetes-associated mortality	From their commencements to February 26, 2014	2 (12)	Five time-series, five case-crossovers and two cohorts	“A high level of O_3 was significantly associated with an increased risk of diabetes-associated mortality.”	RR	1.065 (1.017, 1.115)

B Ergebnisse der Qualitätsbeurteilung der systematischen Reviews basierend auf den AMSTAR2 Kriterien (Heat map of methodology quality assessment for systematic reviews based on AMSTAR2)

Health endpoint	**Study**	**Type**	**Outcome**	**AMSTAR2 items**															
				1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Mortality and hospital admissions	Stieb et al. 2002	SR and meta-analysis	Mortlity	no	no	no	partial yes	no	yes	yes	partial yes	no	no	yes	no	no	yes	no	no
	Bell et al. 2005	SR and meta-analysis	Mortality	no	no	yes	no	no	yes	no	no	no	no	yes	no	no	yes	yes	no
	Smith et al. 2009	SR and meta-analysis	Mortality	no	no	yes	no	no	no	no	partial yes	no	yes	no	no	no	yes	no	yes
	Ji et al. 2011	SR and meta-analysis	Respiratory hospital admissions	no	no	yes	no	no	no	no	partial yes	no	no	yes	no	yes	yes	yes	no
	Atkinson et al. 2012	SR and meta-analysis	Mortality, hospital admissions	no	no	yes	partial yes	no	no	yes	partial yes	no	no	yes	no	no	yes	yes	yes
	Lai et al. 2013	SR and meta-analysis	Health outcomes were related to deaths, birth outcomes and hospital utilization	no	no	yes	no	no	no	no	no	no	no	yes	no	no	yes	yes	yes
	Shang et al. 2013	SR and meta-analysis	Daily mortality, total mortality; respiratory mortality; cardiovascular mortality;	no	no	yes	partial yes	no	no	no	partial yes	no	no	no	no	no	yes	yes	no
	Yan et al. 2013	SR and meta-analysis	Mortality	no	no	yes	partial yes	no	no	no	yes	no	no	yes	no	no	yes	yes	no
	Atkinson et al. 2016	SR and meta-analysis	Mortality: all causes, cardiovascular, respiratory, ischaemic heart disease, lung cancer	no	no	yes	partial yes	no	no	no	partial yes	no	no	yes	no	no	yes	no	yes
	Ab Manan et al. 2018	SR	Hospital admission	no	no	yes	partial yes	no	no	no	partial yes	no	no	NA	NA	no	no	NA	yes
	Requia et al. 2018	SR and meta-analysis	Hospital admissions and mortality on cardiorespiratory diseases and Respiratory diseases	no	no	yes	partial yes	yes	no	partial yes	partial yes	no	no	yes	no	no	yes	yes	no

Health endpoint	Study	Type	Outcome	AMSTAR2 items															
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	Bazyar et al. 2019	SR	Mortality, cardiovascular diseases, respiratory diseases, birth outcomes, neurologic diseases, psychiatric diseases, and emergency hospitalization.	yes	no	no	partial yes	yes	yes	no	partial yes	partial yes	no	NA	NA	no	no	NA	no
	Yang et al. 2019	SR and meta-analysis	Stroke, ischemic heart disease, heart failure, coronary heart disease, myocardial infarction, and overall CVD events (mortality, morbidity, or both)	no	no	yes	partial yes	yes	yes	no	yes	partial yes	no	yes	yes	yes	yes	yes	yes
Respiratory health effects	Minelli et al. 2011	SR	Respiratory function and air way disease	no	no	yes	partial yes	yes	yes	no	partial yes	no	no	NA	NA	yes	yes	NA	yes
	Vawda et al. 2014	SR	Inflammatory and immune response genes and adverse respiratory outcomes	no	no	yes	partial yes	yes	yes	n	no	no	no	NA	NA	yes	yes	NA	yes
	Zheng et al. 2015	SR and meta-analysis	Asthma exacerbations (hospital admission and ER visit).	no	no	yes	partial yes	yes	yes	no	yes	partial yes	no	yes	yes	yes	yes	yes	yes
	Li et al. 2016b	SR and meta-analysis	Risk of COPD exacerbations	no	no	yes	partial yes	yes	yes	no	yes	partial yes	no	yes	yes	yes	yes	yes	yes
	Moore et al. 2016	SR and meta-analysis	COPD exacerbation qualified by hospital admissions	no	no	yes	partial yes	yes	no	no	no	partial yes	no	yes	no	yes	yes	yes	yes
	Rodriguez-Villamizar et al. 2016	SR	Asthma-related hospitalizations in relation to outdoor air pollution (RR or OR)	yes	partial yes	yes	partial yes	yes	yes	partial yes	partial yes	yes	no	NA	NA	yes	yes	NA	yes
	Yang et al. 2016	SR and meta-analysis	Lung cancer	no	no	yes	partial yes	yes	yes	no	partial yes	partial yes	no	yes	yes	yes	yes	yes	yes
	Zhang et al. 2016b	SR and meta-analysis	Hospital utilization for either COPD or asthma	no	no	yes	partial yes	no	no	no	partial yes	no	no	yes	no	no	yes	yes	no

Health endpoint	Study	Type	Outcome	AMSTAR2 items															
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	Hehua et al. 2017	SR and meta-analysis	Asthma or wheeze	no	no	yes	partial yes	no	no	no	partial yes	partial yes	no	yes	yes	yes	yes	no	no
	Nhung et al. 2017	SR and meta-analysis	Hospitalization due to pneumonia	no	no	yes	partial yes	yes	yes	no	yes	no	no	yes	no	no	yes	yes	yes
	Orellano et al. 2017	SR and meta-analysis	Severe asthma exacerbations are defined as an episode of wheezing or shortness of breath that include the need for oral or systemic corticosteroids, and require hospitalization or an emergency room visit.	no	partial yes	yes	partial yes	yes	no	no	partial yes	yes	no	yes	yes	yes	yes	yes	yes
	King et al. 2018	SR	Bronchiolitis admission	yes	partial yes	yes	partial yes	yes	yes	yes	partial yes	yes	no	NA	NA	yes	no	NA	yes
	Luong et al. 2019	SR	Outcome measure related to wheeze associated disorders	no	no	yes	partial yes	yes	yes	no	yes	partial yes	no	yes	yes	yes	yes	no	yes
Neurological health effects	Yang et al. 2014	SR and meta-analysis	Risk of stroke hospitalization andmortality	no	no	yes	partial yes	yes	yes	no	partial yes	partial yes	no	yes	yes	yes	yes	yes	no
	Shah et al. 2015a	SR and meta-analysis	Admission to hospital for stroke or mortality from stroke	yes	partial yes	yes	yes	yes	yes	no	partial yes	partial yes	no	yes	yes	yes	yes	yes	yes
	Hu et al. 2019	SR and meta-analysis	Parkinson's disease	no	no	yes	partial yes	yes	yes	no	yes	partial yes	no	yes	yes	yes	yes	yes	yes
	Kasdagli et al. 2019	SR and meta-analysis	Parkinson's disease	no	no	yes	partial yes	yes	no	no	partial yes	partial yes	no	yes	no	yes	yes	no	yes
	Peters et al. 2019	SR	Incident dementia or incident cognitive decline.	yes	partical yes	yes	partial yes	yes	no	yes	partial yes	yes	no	NA	NA	yes	yes	NA	yes
Cardiovascular and vascular health effects	Mustafic et al. 2012	SR and meta-analysis	Myocardial infarction (MI), heart attack, acute coronary syndrome	no	no	yes	yes	yes	yes	no	partial yes	partial yes	no	yes	yes	yes	yes	yes	yes

Health endpoint	Study	Type	Outcome	AMSTAR2 items															
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	Shah et al. 2013	SR and meta-analysis	Heart failure hospitalisation or heart failure mortality	no	no	yes	partial yes	no	yes	no	partial yes	no	no	yes	no	no	yes	yes	yes
	Teng et al. 2014	SR and meta-analysis	The risk of out-of-hospital cardiac arrest in subjects exposed to the air pollutants is the primary outcome.	yes	partial yes	yes	partial yes	yes	yes	no	yes	yes	no	NA	NA	yes	yes	NA	yes
	Buteau und Goldberg 2016	SR	Heart rate variability (HRV)	no	no	no	partial yes	no	no	yes	yes	no	no	NA	NA	no	yes	NA	yes
	Cai et al. 2016	SR and meta-analysis	Hypertension	no	no	yes	partial yes	yes	yes	no	partial yes	partial yes	no	yes	yes	yes	yes	yes	yes
	Li et al. 2017a	SR and meta-analysis	Non-accidental and cardiovascular mortality	no	no	yes	partial yes	no	yes	no	partial yes	partial yes	no	yes	yes	no	yes	yes	yes
	Shao et al. 2016	SR and meta-analysis	Atrial fibrillation	no	no	yes	partile yes	yes	yes	yes	yes	no	no	yes	no	no	yes	yes	no
	Song et al. 2016	SR and meta-analysis	Change in hospitalization or mortality associated with arrhythmia when air pollution increases above standard levels	yes	partial yes	yes	partial yes	yes	yes	no	partial yes	no	no	yes	no	yes	yes	yes	yes
	Tang et al. 2016	SR	Hospital admissions for venous thrombosis	yes	partial yes	yes	partial yes	yes	yes	no	partial yes	partial yes	no	yes	yes	yes	yes	yes	yes
	Zhao et al. 2017b	SR and meta-analysis	Out-of-hospital cardiac arrest (OHCA)	no	no	yes	partial yes	yes	yes	no	yes	partial yes	no	yes	yes	yes	yes	yes	yes
	Zhao et al. 2017a	SR and meta-analysis	Cardiovascular mortality	no	no	yes	partial yes	no	yes	no	partial yes	no	no	yes	no	no	no	yes	yes
	Yang et al. 2017	SR and meta-analysis	Risk of ventricular arrhythmias in the patients with implantable cardioverter-defibrillator	no	no	yes	yes	yes	yes	no	yes	partial yes	no	yes	yes	yes	yes	yes	yes
	Newell et al. 2018	SR and meta-analysis	Cardiorespiratory health effects	no	partial yes	yes	partial yes	yes	yes	no	partial yes	partial yes	no	yes	yes	yes	yes	yes	yes

Health endpoint	Study	Type	Outcome	AMSTAR2 items															
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	Yang et al. 2018	SR and meta-analysis	Hypertension and blood presure	no	no	yes	partial yes	yes	yes	no	yes	partial yes	no	yes	yes	yes	yes	yes	yes
Reproductive health effects	Hu et al. 2014	SR and meta-analysis	Hypertensive disorders of pregnancy (gestional hypertention, preeclampsia and eclampsia)	no	no	yes	partial yes	yes	yes	no	partial yes	partial yes	no	yes	no	no	yes	yes	no
	Pedersen et al. 2014	SR and meta-analysis	Pregnancy-induced hypertensive disorders (ie, gestational hypertension and preeclampsia as separate outcomes or a combination of these conditions)	no	no	yes	partial yes	no	no	yes	yes	no	no	yes	no	no	yes	yes	yes
	Lafuente et al. 2016	SR	DNA fragmentation, sperm count, sperm motility, and sperm morphology	yes	partial yes	yes	partial yes	yes	yes	no	partial yes	partial yes	no	NA	NA	yes	yes	NA	yes
	Siddika et al. 2016	SR and meta-analysis	The risk of stillbirth, or reported the occurrence of stillbirth	no	no	yes	partial yes	yes	yes	no	partial yes	partial yes	no	yes	yes	yes	yes	yes	yes
	Carre et al. 2017	SR and meta-analysis	Reproductive function (infertility)	no	no	yes	no	no	no	no	partial yes	no	no	NA	NA	no	no	NA	yes
	Conforti et al. 2018	SR	"Fertility outcome"	yes	no	no	partial yes	yes	yes	no	partial yes	partial yes	no	NA	NA	yes	yes	NA	yes
	Jurewicz et al. 2018	SR	Male reproductive outcomes, specifically semen quality	no	no	yes	partial yes	no	yes	no	partial yes	no	no	NA	NA	no	no	NA	yes
	Koman et al. 2018	SR	"Any clinical diagnosis or other continuous or dichotomous scale assessment of preeclampsia or gestational hypertension."	yes	no	yes	no	no	no	no	yes	no	no	NA	NA	no	no	NA	yes

Health endpoint	Study	Type	Outcome	AMSTAR2 items															
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
	Elshahidi 2019	SR and meta-analysis	Gestational diabetes mellitus (GDM)	no	no	yes	partial yes	no	no	no	partial yes	partial yes	no	yes	no	no	yes	no	yes
Birth outcomes	Bonzini et al. 2010	SR and meta-analysis	Preterm delivery, low birth weight, and/or Small for Gestational Age (SGA)	no	no	yes	no	yes	no	yes	partical yes	no	no	NA	NA	no	no	NA	yes
	Shah und Balkhair 2011	SR	Birth outcomes such as low birth weight (LBW), preterm birth (PTB) and small for gestational age (SGA) births, birth weight (BW) and gestational age (GA)	no	partial yes	yes	partial yes	yes	yes	yes	yes	yes	no	NA	NA	yes	yes	NA	yes
	Vrijheid et al. 2011	SR and meta-analysis	Congenital anomalies	no	no	yes	partial yes	no	no	no	yes	no	no	yes	no	no	no	yes	yes
	Stieb et al. 2012	SR and meta-analysis	Outcome of preterm birth (o37 weeks gestation)/gestational age, birth weight/low birth weight (LBW) (o2500 g)/small for gestational age (SGA)/ intrauterine growth restriction (IUGR) (o10th percentile for gestational age)	no	no	yes	partial yes	yes	yes	no	yes	partial yes	no	yes	yes	yes	yes	yes	yes
	Chen et al. 2014	SR and meta-analysis	Congenital anomalies	no	partial yes	yes	no	no	no	no	yes	no	no	yes	no	no	yes	no	yes
	Rao et al. 2016	SR and meta-analysis	Orofacial cleft anomalies; Cleft palate (CP), cleft lip (CL), cleft lip with or without palate (CL/P)	no	no	yes	partial yes	yes	no	no	partial yes	partial yes	no	no	no	no	yes	no	yes
	Guo et al. 2019	SR and meta-analysis	Adverse birth outcomes; preterm birth (PTB), birth weight/low birth weight (LBW), small for gestational age (SGA)	yes	partial yes	yes	partial yes	yes	no	no	partial yes	yes	no	yes	yes	yes	yes	yes	yes

Health endpoint	Study	Type	Outcome	AMSTAR2 items															
				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Mental health	Flores-Pajot et al. 2016	SR and meta-analysis	Autism spectrum disorder (ASD), or autism	no	no	yes	partial yes	no	no	no	yes	partial yes	no	yes	yes	no	yes	yes	no
	Zhao et al. 2018	SR	Any mental and behavioral disorder.	yes	partial yes	yes	partial yes	no	no	no	yes	yes	no	NA	NA	yes	yes	NA	yes
	Zeng et al. 2019		Depression	no	no	yes	partial yes	yes	yes	no	partial yes	partial yes	no	yes	yes	no	yes	no	yes
Endocrine health effects	Li et al. 2014	SR and meta-analysis	Diabetes-associated mortality	yes	partial yes	yes	partial yes	yes	yes	no	partial yes	partial yes	no	yes	yes	yes	yes	yes	yes
	An et al. 2018	SR	Body weight status including overweight/obesity measured by body mass index (BMI, kg/m2), waist circumference (WC), waist-to-hip ratio (WHR), or body fat	no	no	yes	partial yes	yes	no	yes	yes	partial yes	no	NA	NA	yes	yes	NA	yes
Dermatological health effects	Kramer und Behrendt 2019	SR	Atopic eczema	no	no	yes	no	no	no	no	yes	partial yes	np	NA	NA	yes	yes	NA	yes
Rheumatic health effects	Dzhambov et al. 2016	SR	Rheumatoid arthritis morbidity	no	partial yes	yes	partile yes	yes	yes	no	partial yes	partial yes	no	NA	NA	yes	yes	NA	no

C Überprüfung der biologischen Plausibilität einer kausalen Assoziation zwischen Ozonexposition und COPD durch Einbeziehung von experimentellen Studien durch Systematic Mapping

Identification		**Population**	**Exposure (ozone)**	**Comparison**	**Results of the study**	**Conclusion of the study**
Study	Journal	Description	Description	Description	Description	Description
Animal study						
Triantaphyllopoulos et al. 2011	American journal of physiology. Lung cellular and molecular physiology	Pathogen-free, 10- to 12-wk-old male BALB/c mice (Harlan) each level of ozone exposure (n = 9 in each group) compared with the air-exposed mice (n = 8)	“Ozone produced by an ozonizer (Sander 500 ozonizer; Erwin Sander, Uetze-Eltze, Germany) mixed with air for 3 h at a concentration of 2.5 parts per million (ppm) in a sealed Perspex container”	“Ozone exposure was carried out in three groups: 1) single exposure of 3 h; 2) two exposures (every 3 days) per week over 3 wk; and 3) two exposures (every 3 days) per week over 6 wk. Control animals were exposed to air over the equivalent period or over a 3-wk period”	“Compared with air-exposed mice, the increase in neutrophils in bronchoalveolar lavage fluid and lung inflammation index was greatest in mice exposed for 3 and 6 wk. Lung volumes were increased in 3- and 6-wk-exposed mice but not in single-exposed. Alveolar space and mean linear intercept were increased in 6- but not 3-wk-exposed mice. Caspase-3 and apoptosis protease activating factor-1 immunoreactivity was increased in the airway and alveolar epithelium and macrophages of 3- and 6-wk-exposed mice. Interleukin-13, keratinocyte chemoattractant, caspase-3, and IFN-gamma mRNA were increased in the 6-wk-exposed group, but heme oxygenase-1 (HO-1) mRNA decreased. matrix metalloproteinase-12 (MMP-12) and caspase-3 protein expression increased in lungs of 6-wk-exposed mice. Collagen area increased and epithelial area decreased in airway wall at 3- and 6-wk exposure.”	“Exposure of mice to ozone for 6 wk induced a chronic inflammatory process, with alveolar enlargement and damage linked to epithelial apoptosis and increased protease expression.”

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Li et al. 2016a	American journal of respiratory cell and molecular biology	Pathogen-free, 8-10 weeks old male C57/BL6 mice	Mice were exposed to ozone produced from a generator (Model 300, AB Aqua Medic GmbH, Bissendorf, Germany), mixed with air for 3 hours at a concentration 2.5 ppm in a sealed Perspex container	"Control animals were exposed to filtered air only. The experiment was carried out in 8 groups." For groups 1-4, the mice were injected intraperitoneally with either NaHS (Sodium hydrosulfide, 2 mg/kg; dissolved in phosphate-buffered saline, PBS) or vehicle alone (PBS) one hour before each exposure to either ozone or air, two exposures (every 3 days) per week for 6 weeks. For groups 5-8, following the cessation of ozone/air exposure, the mice were injected intraperitoneally with either NaHS (2 mg/kg; dissolved in PBS) or vehicle alone (PBS), two times (every 3 days) per week for 6 weeks."	The ozone-exposed mice "developed emphysema, measured by micro-computed tomography and histology, airflow limitation, measured by the forced maneuver system, and increased lung inflammation with augmented IL-1beta, IL-18, and matrix metalloproteinase-9 (MMP-9) gene expression. Ozone-induced changes were associated with increased Nod-like receptor pyrin domain containing 3 (NLRP3)-caspase-1 activation and p38 mitogen-activated protein kinase phosphorylation and decreased Akt phosphorylation."	"NaHS both prevented and reversed lung inflammation and emphysematous changes in alveolar space. In contrast, NaHS prevented, but did not reverse, ozone-induced airflow limitation and bronchial structural remodeling. NaHS administration prevented and partially reversed ozone-induced features of lung inflammation and emphysema via regulation of the NLRP3-caspase-1, p38 mitogen-activated protein kinase, and Akt pathways."
Kirkham et al. 2011	American journal of respiratory and critical care medicine	Pathogen-free, 6- to 8-week old male BALB/c mice 6-8 mice in each treatment group (air versus ozone)	"Exposed to 2.5 ppm ozone for 3 hours in a sealed Perspex container either once (acute) or every 3 days for 6 weeks (chronic)"	"Control animals were exposed to air over the equivalent period."	"Ozone-exposed mice similarly exhibited increased antibody titers to carbonyl-modified protein, as well as activated antigen-presenting cells in lung tissue and splenocytes sensitized to activation by carbonyl-modified protein."	"Carbonyl-modified proteins, arising as a result of oxidative stress, promote antibody production, providing a link by which oxidative stress could drive an autoimmune response in COPD."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Avdalovic et al. 2012	Anatomical record	California National Primate Research Center (CNPRC) colony-born rhesus macaques (Macaca mulatta) 48 infant rhesus monkeys	Ozone was delivered for 8 hr/day at 0.5 ppm for 5 contiguous days (n = 24) "…exposed infant rhesus monkeys biweekly to 5, 8 hours/day, cycles of 0.5 ppm ozone with or without house dust mite allergen from 1 to 3 or 1 to 6 months of age."	At 1 month of age 48 infant rhesus monkeys (30 days old) were exposed to 5 or 11 episodes of filtered air (FA) (n= 12), Dermatophagoides farinaeaerosol (n = 12), ozone (ozone) (n = 12), or Dermatophagoides farinae+ ozone (n = 12) (5 days followed by 9 days of FA for a total of 2 weeks).	Monkeys exposed to ozone alone or ozone combined with allergen had statistically larger alveoli that were less in number at 3 months of age. Alveolar capillary surface density was also decreased in the ozone exposed groups at 3 months of age. At 6 months of age, the alveolar number "was similar between treatment groups and was associated with a significant rise in alveolar number from 3 to 6 months of age in the ozone exposed groups. This increase in alveolar number was not associated with any significant increase in microvascular growth as measured by morphometry or changes in angiogenic gene expression."	"Inhalation of ozone during infancy alters the appearance and timing of alveolar growth and maturation."
Deng et al. 2013	Biological & pharmaceutical bulletin	Fifty adult male Kunming mice weighing 30-35 g	Infused with mixed gas containing 4.0 ppm of ozone and fresh air. During 5 consecutive days of intragastric administration, 10 min every afternoon (2:00–4:00 p.m.) "Ozone was generated by directing an air source through an ozone generator (JC-006, Ruda shiji Co., Ltd., Beijing, China)."	Randomly divided into the following five groups (10 mice per group): Control group, Model group, Procaterol group, Compound T group and Compound H group	Results indicated that (1) no drug showed severe toxicity in this study; (2) ozone exposure induced airway inflammation and Airway hyperresponsiveness (AHR); "(3) intragastric treatment with procaterol and Compound T achieved potent therapeutic effects, but Compound H did not show any therapeutic effect; (4) the NF-kappaB pathway was involved in both the pathogenic mechanisms of ozone and therapeutic mechanisms of procaterol and Compound T; (5) however, the in vivo effect of Compound T was not caused by its inhibitory activity on CD38. "	"Procaterol and two synthetic CD38 inhibitors (Compounds T and H) might have therapeutic effects on the ozone-induced AHR mice model, and the nuclear factor-kappaB (NF-kappaB) pathway and the CD38 enzymatic activity might be involved in the mechanisms … procaterol and Compound T are potentially good drugs to treat asthma and COPD complicated with ozone exposure."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Zhang et al. 2016a	Biomedicine & pharmacotherapy	Pathogen-free, 10 weeks old male C57/BL6 mice, weighting 18–22 g	Animals were exposed to ozone produced from an ozoniser (Model 500 Sander Ozoniser, Germany), "mixed with air, for 3 h at a concentration 2.5 ppm in a sealed Perspex container, twice a week for 6 weeks. Control animals received medical air only over the equivalent period."	"According to random number table, mice are divided into 4 groups: air-exposed + PBS-treated model, ozone-exposed + PBS-treated model, air-exposed + IL-17mAb-treated model, ozone-exposed + IL-17mAb-treated model."	"The administration of IL-17mAb reduced the ozone-induced increases in total cells, especially neutrophils; decreased levels of cytokines, including IL-8 in Bronchoalveolar lavage fluid (BALF), IL-8 and IL-17A in serum; mitigated the severity of airway hyperresponsiveness; attenuated lung inflammation scores and histologic analysis confirmed the suppression of lung inflammation, compared with the administration of a control PBS. Exposure to ozone results in increases in IL-17A production rate, mRNA and protein levels of IL-17A and the protein level of GR. These effects were halted and reversed by IL-17mAb treatment. Furthermore, IL-17mAb also reduced the phosphorylation of p38MAPK."	"IL-17mAb may be a useful therapy in ozone-related diseases, including COPD."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Toward und Broadley 2002	British journal of pharmacology	Groups of six male Dunkin-Hartley guinea-pigs, weighing 300 ± 400 g were used throughout	The effects of ozone inhalation (90 min, 2.15 ± 0.05 p.p.m.) and their medication by dexamethasone (20 mg/kg) or the phosphodiesterase-4 inhibitor, rolipram (1 mg/kg), administered (i.p.) 24 and 0.5 h before and 24 h after ozone exposure were examined in conscious Guinea pigs. Groups of six guinea-pigs were box-exposed for 90 min to ozone generated via medic-air (0.35 l/min, 18.8 - 23.5 % oxygen in nitrogen) passed through an ozonizer (model 100; Sander, Frankfurt, Germany) maintain a constant level of ozone 2.15 ± 0.05 ppm. Control animals were exposed for 90 min to medic-air.	Medic-air, ozone, ozone & dexamethasone, ozone & rolipram	Ozone caused an early-phase bronchoconstriction (EPB) as a fall in specific airways conductance (sG(aw)) measured by whole body plethysmography, "followed at 5 h by a late-phase bronchoconstriction (LPB) and increased respiratory rate. Rolipram did not alter this profile but dexamethasone inhibited the EPB." Airway hyperreactivity to inhaled histamine (1 mM, 20 s) occurred at 0.5, 2, 12, 24 and 48 h after ozone inhalation, the 2 h change being abolished by rolipram and dexamethasone. Bronchoalveolar lavage fluid (BALF) macrophages, eosinophils and neutrophils were significantly ($P<0.05$) elevated at 12, 24 and 48 h after ozone exposure, the 48 h influx being significantly attenuated ($P < 0.05$) by rolipram and dexamethasone. "BALF nitric oxide (NO) metabolites decreased 0.5 h after ozone exposure by 52 %, recovered at 2 h and significantly increased at 12 (101 %) and 24 h (127 %). The elevated NO was unaffected by rolipram or dexamethasone." "Lung oedema, measured from wet/dry weight differences, was significant 12, 24 and 48 h after ozone exposure, the latter being significantly attenuated ($P < 0.05$) by rolipram and dexamethasone. "	Oxidative stress induced by ozone exposure of conscious guinea-pigs causes an EPB and LPB. "Ozone exposure of guinea-pigs produced features common to COPD. Although rolipram and dexamethasone did not affect the airway function changes, they inhibited the inflammation, airway hyperreactivity and oedema."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Gao et al. 2015	Clinical science	Eight-week-old male C57BL/6 mice	Exposed to ozone at a concentration of 3 ppm. for 3 h a day, twice a week for a period of 1, 3 or 6 weeks Control animals were exposed to normal air.	Air, ozone	Human Klotho(KL) expression was decreased in the lungs of smokers and further reduced in patients with COPD. Similarly, 6 weeks of exposure to ozone "decreased KL levels in airway epithelial cells. CSE and TNFalpha (tumour necrosis factor alpha) decreased KL expression and release from airway epithelial cells, which was associated with enhanced pro-inflammatory cytokine expression. Moreover, KL depletion increased cell sensitivity to cigarette smoke-induced inflammation and oxidative stress-induced cell damage. These effects involved the NF-kappaB (nuclear factor kappaB), MAPK (mitogen-activated protein kinase) and Nrf2 (nuclear factor erythroid 2-related factor 2) pathways. "	"Human Klotho (KL) is an anti-aging protein that protects cells against inflammation and damage) … 6 weeks of exposure to ozone decreased KL levels in airway epithelial cells … Reduced KL expression in COPD airway epithelial cells was associated with increased oxidative stress, inflammation and apoptosis."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Wang et al. 2017	Clinical science	C57/BL6mice (6 weeks old)	Mice were exposed to ozone for 2 days per week (3 ppm, 3 h/day) for a period of 1 or 3 weeks	Air, ozone	Reticular basement membrane (RBM) thickness and E-cadherin and alpha-smooth muscle actin (alpha-“SMA) expression were determined in mice airways. Effects of cigarette smoke extract (CSE) and inflammatory factors on NGAL expression in human neutrophils as well as the effects of NGAL on airway structural cells was assessed. NGAL was mainly distributed in neutrophils and enhanced in lung tissues of both COPD patients and BALF of ozone-treated mice. We showed decreased E-cadherin and increased alpha-SMA expression in bronchial epithelium and increased RBM thickness in ozone-treated animals. In vitro, CSE, IL-1beta and IL-17 enhanced NGAL mRNA expression in human neutrophils. NGAL, in turn, down-regulated the expression of E-cadherin and up-regulated alpha-SMA expression in 16HBE cells via the WNT/glycogensynthase kinase-3beta (GSK-3beta) pathway. Furthermore, NGAL promoted the proliferation and migration of human bronchial smooth muscle cells (HASMCs).”	“Neutrophil gelatinase-associated lipocalin (NGAL) from neutrophils may drive COPD epithelial-mesenchymal transition (EMT) … NGAL was mainly distributed in neutrophils and enhanced in lung tissues of both COPD patients and BALF of ozone-treated mice … We showed decreased E-cadherin and increased alpha-SMA expression in bronchial epithelium and increased RBM thickness in ozone-treated animals. … The present study suggests that elevated NGAL promotes COPD airway remodelling possibly through altered EMT. NGAL may be a potential target for reversing airway obstruction and remodelling in COPD.”

Identification		**Population**	**Exposure (ozone)**	**Comparison**	**Results of the study**	**Conclusion of the study**
Wiegman et al. 2014	Clinical science	C57BL/6 mice (6 weeks old; Harlan) n=8 mice per group	"Exposed to ozone (model 500 Ozoniser; Erwin Sander) mixed with air to a 3 ppm. concentration. Mice were exposed for 3 h a day, twice a week for a period of 1, 3 or 6 weeks (n=8 mice per group). Control groups were exposed to normal air in an identical experimental setup (n=8 mice per group)."	Air, ozone "Mice were exposed for 3 h a day, twice a week for a period of 1, 3 or 6 weeks (n=8 mice per group). Control groups were exposed to normal air in an identical experimental setup (n=8 mice per group)."	"BAL total cell counts were elevated at all of the time points studied. This was associated with increased levels of chemokines and cytokines in all ozone-exposed groups, indicating the presence of a persistent inflammatory environment in the lung. Increased inflammation and Lm (mean linear intercept) scores were observed in chronic exposed mice, indicating emphysematous changes were present in lungs of chronic exposed mice. The antioxidative stress response was active (indicated by increased Nrf2 activity and protein) after 1 week of ozone exposure, but this ability was lost after 3 and 6 weeks of ozone exposure. The transcription factor HIF-1alpha was elevated in 3- and 6-week ozone-exposed mice and this was associated with increased gene expression levels of several HIF-1alpha target genes including HDAC2 (histone deacetylase 2), Vegf (vascular endothelial growth factor), Keap1 (kelch-like ECH-associated protein 1) and Mif (macrophage migration inhibitory factor)."	"HDAC2 protein was found to be phosphorylated and carbonylated in nuclear and cytoplasm fractions, respectively, and was associated with a decrease in DNA-binding activity and protein expression of HDAC2. Decreased HDAC2 activity, most likely a direct result of protein modification, in combination with the loss of the antioxidative stress response and activation of the HIF-1alpha pathway, contribute to the inflammatory response and emphysema observed in ozone-exposed mice."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Yoon et al. 2007	Environmental health perspectives	Male (6–8 weeks old, 20 – 25 g) C57BL/6J (Mmp7+/+) and B6.129-Mmp7tm1Lmm/J (Mmp7–/–), FVB/NJ (Mmp9+/+), and FVB.Cg-Mmp9tm1Tvu/J (Mmp9–/–) mice (n = 8–10/group)	"Mice were exposed continuously to 0.3 ppm ozone for 6, 24, 48, or 72 h. ozone was generated from ultra-high purity air (< 1 ppm total hydrocarbons; National Welders, Inc., Raleigh, NC) using a silent arc discharge ozone generator (Model L-11; Pacific Ozone Technology, Benecia, CA). … Parallel exposure to filtered air was conducted in a separate chamber for 48 hr."	Air, ozone	"Relative to air-exposed controls, MMP-9 activity in bronchoalveolar lavage fluid (BALF) was significantly increased by ozone exposure in Mmp9(+/+) mice. Ozone-induced increases in the concentration of total protein (a marker of lung permeability) and the numbers of neutrophils and epithelial cells in BALF were significantly greater in Mmp9(-/-) mice compared with Mmp9(+/+) mice. Keratinocyte-derived chemokine (KC) and macrophage inflammatory protein (MIP)-2 levels in BALF were also significantly higher in Mmp9(-/-) mice than in Mmp9(+/+) mice after ozone exposure, although no differences in mRNA expression for these chemokines were found between genotypes. Mean BALF protein concentration and numbers of inflammatory cells were not significantly different between Mmp7(+/+) and Mmp7(-/-) mice after ozone exposure."	"Matrix metalloproteinases (MMPs) have been implicated in the pathogenesis of oxidative lung disorders including acute lung injury, asthma, and chronic obstructive pulmonary disease. … Results demonstrated a protective role of MMP-9 but not of MMP-7, in ozone-induced lung neutrophilic inflammation and hyperpermeability. The mechanism through which Mmp9 limits ozone-induced airway injury is not known but may be via posttranscriptional effects on proinflammatory CXC chemokines including KC and MIP-2."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Sherwood et al. 1986	Environmental research	Male specific pathogen-free (SPF) Sprague-Dawley rats weighing 130-150 g	"Ten days after infection half the rats were exposed to atmospheres of air and half to 0.64 ppm ozone for 4 weeks." Ozone was generated by silent electrical discharge. Ozone concentrations were monitored continuously and recorded with a Dasibi Model 1003AH (Dasibi Environmental). The instrument was calibrated using the ultraviolet photometer method of McElroy (1979). Actual exposure concentrations were 0.63 ± 0.02 ppm. The remaining rats were placed in identical chambers and exposed to filtered air.	Control air, Pab air control ozone, PAB ozone	"Measurement of lysozyme in individual rat AM in situ showed a significant decrease in cell size and enzyme content in ozone-exposed uninfected animals. Cell size and enzyme content of ozone-exposed animals with CPI were further reduced."	A synergistic effect between ozone exposure and chronic infection.
Pinart et al. 2014	European journal of pharmacology	Pathogen-free, 10–12 weeks old male C57/BL6J mice (Harlan, UK) andgender-matched MKP-1 (-/-) mice (Kennedy Institute, Imperial College, UK)	MKP-1 / and C57/BL6J were "investigated and received ozone twice a week for a period of 6 weeks (a total of 12 exposures). Ozone was generated from an ozoniser (Model 500 Sander Ozoniser, Germany), mixed with air for 3 h at 2.5 parts per million (ppm) in a sealed Perspex container. Control animalsreceived medical air only over the equivalent period.	"Ozone exposure was carried out in 3 groups: (i) ozone and vehicle, (ii) ozone and 0.1 mg/kg dexamethasone and (iii) ozone and 2 mg/kg dexamethasone. During the final 4 weeks of ozone exposure, animals received either dexamethasone or vehicle 2 h prior to each exposure to ozone (i.e. 8 injections in all)." Control animals received medical air only over the equivalent period."	In "ozone-exposed C57/BL6J mice, bronchial hyperresponsiveness (BHR) was not inhibited by both doses of dexamethasone, but in MKP-1(-/-) mice, there was a small inhibition by high dose dexamethasone (2 mg/kg). There was an increase in mean linear intercept after chronic ozone exposure in both strains which was corticosteroid insensitive. There was lesser inflammation after low dose of dexamethasone in MKP-1(-/-) mice compared to C57/Bl6J mice. Epithelial and collagen areas were modulated in ozone-exposed MKP-1(-/-) mice treated with dexamethasone compared to C57/Bl6J mice. MKP-1 regulated the expression of MMP-12, IL-13 and KC induced by ozone but did not alter dexamethasones effects."	"Chronic exposure to ozone leads to a corticosteroid-insensitive model of BHR, emphysema and lung inflammation. Mitogen-activated protein kinase phosphatase-1 (MKP-1) may increase the expression of MMP-12 and IL-13 in the presence of ozone exposure, but is not involved in the effect of corticosteroids. However, MKP-1 may modulate to a small extent the effects of corticosteroids on ozone induction of BHR, and inflammation, with a greater contribution to the epithelial and collagen changes in the airways, representative of the remodelling process.

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Damera et al. 2010	Experimental lung research	BALB/c mice (n = 5/cohort) were exposed to ozone (100 ppb) or forced air (FA) for 4 hours mice between 6 and 7 weeks of age	Ozone was generated by directing an air source through an AQUA-FLO ozone generator (model CD05; Aqua-Flo, Baltimore, MD), upstream of the exposure chamber. "The ozone-oxygen mixture was metered into the inlet air stream, and ozone concentrations were monitored continuously within the chamber with an ozone monitor (model 202; 2B Technologies, Golden, CO). Groups of mice (n = 5) were exposed to 100 ppb ozone for 4 hours during which time they did not have access to food and water. The control mice received forced air and were deprived of food and water for 4 hours."	"Groups of mice (n = 5) were exposed to 100 ppb ozone for 4 hours during which time they did not have access to food and water. The control mice received forced air and were deprived of food and water for 4 hours. "	"Ozone selectively enhanced bronchoalveolar lavage (BAL) levels of killer cells (KCs; 6 ± 0.9-fold), interleukin-6 (IL-6; 12.7 ± 1.9-fold), and tumor necrosis factor (TNF; 2.1 ± 0.5-fold) as compared to cohorts exposed to FA. Additionally, ozone increased BAL neutrophils by 21 % ± 2 % with no significant (P > 0.05) changes in other cell types. MANS, BIO-11000, and BIO-11006 significantly reduced ozone-induced KC secretion by 66 % ± 14 %, 47 % ± 15 %, and 71.1 % ± 14 %, and IL-6 secretion by 69 % ± 12 %, 40 % ± 7 %, and 86.1 % ± 11 %, respectively. Ozone-mediated increases in BAL neutrophils were reduced by MANS (86 % ± 7 %) and BIO-11006 (84 % ± 2.5 %), but not BIO-11000."	"Inhibition of myristoylated alanine-rich C kinase substrate (MARCKS), an 82-kDa protein with multiple biological roles, could inhibit ozone-induced leukocyte trafficking and cytokine secretions … These studies identify for the first time the novel potential of MARCKS protein inhibitors in abrogating ozone-induced increases in neutrophils, cytokines, and chemokines in BAL fluid."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Hicks et al. 2010b	Inflammation	Thirty-six male Cynomolgus monkeys (Macaca fascicularis; 3.5 – 7 kg; Lovelace Respiratory Research Institute (LRRI))	Ozone was generated using two OREC generators (Ozone Research & Equipment Corporation, Phoenix, AZ) delivered to the inlet of a H2000 whole body exposure chamber. Ozone concentration was monitored every 10 min using an API Ozone Monitor (Model 450, Advanced Pollution Instrumentation, Inc., San Diego, CA). Ozone concentration in the control chamber was monitored every 50 min. Monkeys were exposed to a target ozone concentration of 1 ppm (or sham exposed to filtered air) for 6 h+T90 (time for concentration to reach 90 % of equilibrium, determined in preliminary testing to be 8 min) in whole body stainless steel and glass H2000 or H1000 inhalation chambers. … In the single challenge experiments, animals were exposed once to ozone or filtered air (n=12 per group) for 6 h. … In the repeat challenge studies using a separate group of animals, the first exposure was performed as outlined above (n=4 exposed to air and n=8 exposed to ozone; termed Phase 1) and following a 2 weeks rest period all animals were challenged with ozone (termed Phase 2).”	Two studies were conducted using 24 and 12 animals, respectively. The first was a characterization of a single ozone challenge and the second was a study of the effects of repeat challenge.	“Ozone challenge evoked BAL cellular inflammation and increases in total protein, alkaline phosphatase and cytokines. Lung histology revealed cellular inflammation and epithelial necrosis. Gene expression profiling identified oxidative phosphorylation, immune response and cell adhesion pathways altered in response to ozone, with common and unique profiles in lung and blood. Lipocalin 2, CD177, the FK-506 and S100A8 binding proteins and ST-2 represent novel peripheral biomarkers of ozone toxicity. Repeat ozone challenge evoked reproducible inflammation but attenuated cell damage.”	“Repeat ozone challenge evoked reproducible inflammation but attenuated cell damage.”

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Dye et al. 2017	Inhalation toxicology	Fisher (F344), Sprague-Dawley (SD) and Wistar (WIS) male and female neonatal rat pups F344 n = 3–4 pups/group, SD and WIS n = 7–8 pups/group	Ozone was generated from oxygen using a silent arc discharge ozone generator (model 3V1, Or Research Equipment Co., Phoenix, AZ) acute ozone exposure (1 ppm x 2 h) on post-natal day (PND) 14, 21, or 28.	“F344, SD and WIS neonatal pups were exposed to either air or 1.0 ppm ozone (×2 h without their dams) at post-natal day 14 (PND14, pre-weaning), PND21 (weaning), or PND28 (postweaning). PND14 and PND21 pups were exposed in sets of 10–12 animals per exposure group. Older animals (PND 28) were exposed in sets of 6–8 animals for each exposure. Sets of PND14, PND21 or PND28 animals were randomly derived from multiple litters for each exposure. Exposures for the three age comparisons were performed between the hours of 8 am and 12 pm, Monday–Friday, on a revolving schedule to control for potential diurnal effects.”	“Post-ozone exposure, data suggest that: (1) the youngest (PND14) pups were the most adversely affected; (2) neonatal SD and WIS pups, especially females, were more prone to ozone effects than males of the same age and (3) F344 neonates (females and males) were less susceptible to oxidative lung insult, not unlike F344 adults	“Findings suggest that strain- and sex-based differences in antioxidant response to ozone are already present early in life; with F344 pups being comparatively resilient and SD and WIS pups (especially females) more susceptible, to ozone. … Differences in antioxidant levels and responsiveness between sexes and strains and at different periods of development may provide a basis for assessing later life health outcomes - with implications for humans with analogous genetic or dietary-based lung antioxidant deficits.”

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
March et al. 2002	Inhalation toxicology	Female B6C3F1 mice	Exposed to filtered air (FA), ozone (0.3 ppm), cigarette smoke (CS) (250 mg total particulate material [TPM]/m^3), or ozone in combination with CS (CSozone) for up to 32 wk “Female B6C3F1 mice were whole-body exposed either to filtered air (FA) or to mainstream CS at a concentration of 250 mg total particulate material/m(3) for 6 h/day, 5 days/wk for 15 or 32 wk.”	Exposed to filtered air (FA), ozone (0.3 ppm), CS (250 mg total particulate material [TPM]/m^3), or ozone in combination with CS (CSozone) for up to 32 wk	“After 32 wk of exposure, CS with or without concurrent ozone exposure produced stereologic evidence of emphysema as previously described. Concurrent ozone exposure did not worsen any of these parameters, nor did ozone by itself cause stereologic changes that were consistent with emphysema. The ozone exposure caused only slight elevations of BALF macrophages, while CS exposure caused marked increases in the numbers of both BALF macrophages and neutrophils. Neutrophils in the BALF in response to CS exposure were also more numerous at 32 wk than at 15 wk. Exposure to CS caused an increase in BALF total protein, lactate dehydrogenase (LDH), alkaline phosphatase, and IL-1beta. After 32 wk, CS exposure was associated with decreased superoxide production from isolated alveolar macrophages. The CS exposure elevated BALF total glutathione primarily at 15 wk.”	Concurrent ozone “exposure did not worsen any of these parameters, nor did ozone by itself cause stereologic changes that were consistent with emphysema. The ozone exposure caused only slight elevations of BALF macrophages, … Overall, ozone had little effect on endpoints that were significantly affected by CS exposure. We conclude that concurrent ozone exposure has no effect on the induction of emphysema by CS in this animal model.”
Liu et al. 2016	International Journal of Clinical and Experimental Medicine	Balb/c mice (20 g)	The mice were kept in a tightly sealed chamber with whole-body exposure to ozone at a concentrations of 1, 5 ppm for 30 min/day for consecutive 5 days (n=6/group), while they were awake and breathing spontaneously in the chamber. The mice were kept in a tightly sealed chamber with whole-body exposure to ozone at a concentrations of 1, 5 ppm for 30 min/day for consecutive 5 days (n=6/group), while they were awake and breathing spontaneously in the chamber.	Control, ozone, emodin, ozone+emodin, ozone+GC groups (GC was not specified in the study)	Emodin inhibited airway resistance, inflammatory cell infiltration, Th1 and Th17 production. On bronchial epithelial cells (BECs), Emodin displayed an obvious cytotoxicity over 20 mu g/mL. Emodin inhibited TGF-beta production and promoted Polyethylenglycol (PGE)2 production under ozone stress. Emodin also inhibited H-3-Udr and LDH secretion and promoted catalase activity.	Emodin has strong anti-AHR effects, which was related with improvement of epithelial protection against injury.

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Wiegman et al. 2015	The Journal of allergy and clinical immunology	Male C57BL/6 mice (6 weeks old, Harlan, Wyton, UK), were housed in groups of 5 for the duration of the experiment.	Mice were exposed to ozone (model 500 Ozoniser, Sander, Wuppertal, Germany) mixed with air (3ppm concentration). Mice were exposed for 3 hours a day, 2 times a week for a period of 1 or 6 weeks. Control groups were exposed to normal air.	Air + dTPP, air + MitoQ ozone + dTPP, ozone + MitoQ dTP, decyltriphenylphosphonium bromide; MitoQ is a combination of ubiquinone	Mice exposed to ozone, a source of oxidative stress, had lung inflammation and AHR associated with mitochondrial dysfunction and reflected by decreased mitochondrial membrane potential (DeltaPsim), increased mitochondrial oxidative “stress, and reduced mitochondrial complex I, III, and V expression. Reversal of mitochondrial dysfunction by the mitochondria-targeted antioxidant MitoQ reduced inflammation and AHR.”	Mice exposed to ozone “had lung inflammation and AHR associated with mitochondrial dysfunction and reflected by decreased mitochondrial membrane potential (DeltaPsim), increased mitochondrial oxidative stress, and reduced mitochondrial complex I, III, and V expression. … Mitochondrial dysfunction in patients with COPD is associated with excessive mitochondrial ROS levels, which contribute to enhanced inflammation and cell hyperproliferation. Targeting mitochondrial ROS represents a promising therapeutic approach in patients with COPD.”

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Yonchuk et al. 2017	The Journal of pharmacology and experimental therapeutics	C57BL/6J mice (25-30 g, Jackson Laboratory, Bar Harbor, ME) and Han Wistar rats (290-370 g, Charles River Laboratories, Wilmington, MA)	Han Wistar rats were exposed to ozone generated by an Oxycycler ozonator (Biospherix Inc., Lacona, NY) in which compressed air and oxygen were passed through the ozonator and flowed into a plexiglass chamber containing the animals. Rats were exposed to 1 ppm of ozone for a 3 hours period.	Twenty-four hours prior to ozone injury, rats received a single oral administration of vehicle (0.9 % dimethylsulfoxide (DMSO), 7 % dimethylacetoacetamide (DMA), 10 % Cremophor El, 82.1 % water) or compound.	Nrf2 (nuclear factor (erythroid-derived 2)-like 2) activator, 3-(pyridin-3-ylsulfonyl)-5-(trifluoromethyl)-2H-chromen-2-one “(PSTC), induced Nrf2 nuclear translocation, Nrf2-regulated gene expression, and downstream signaling events, including induction of NAD(P)H:quinone oxidoreductase 1 (NQO1) enzyme activity and heme oxygenase-1 protein expression, in an Nrf2-dependent manner. As a marker of subsequent functional activity, PSTC restored oxidant (tert-butyl hydroperoxide)-induced glutathione depletion. The compound's engagement of the Nrf2 signaling pathway translated to an in vivo setting, with induction of Nrf2-regulated gene expression and NQO1 enzyme activity, as well as restoration of oxidant (ozone)-induced glutathione depletion, occurring in the lungs of PSTC-treated rodents. Under disease conditions, PSTC engaged its target, inducing the expression of Nrf2-regulated genes in human bronchial epithelial cells derived from patients with chronic obstructive pulmonary disease, as well as in the lungs of cigarette smoke-exposed mice. Subsequent to the latter, a dose-dependent inhibition of cigarette smoke-induced pulmonary inflammation was observed. Finally, in contrast with bardoxolone methyl and sulforaphane, PSTC did not inhibit interleukin-1beta-induced nuclear factor-kappaB translocation or insulin-induced S6 phosphorylation in human cells, emphasizing the on-target activity of this compound.”	Oxidant (ozone)-induced glutathione depletion “Selective Nrf2 activator that offers protection against pulmonary oxidative stress in several cellular and in vivo models.”

Identification		**Population**	**Exposure (ozone)**	**Comparison**	**Results of the study**	**Conclusion of the study**
Sun et al. 2017	Journal of visualized experiments	House pathogen-free, 7- to 9-week-old female BALB/c mice	Generate ozone with an electric generator in a sealing acrylic (e.g. Perspex) box "Place the mice into the box when the level of ozone reaches 2.5 ppm. Keep the mice in the box for 3 h each time to expose them to ozone … Give two ozone exposures (each exposure lasting 3 h) per week (once every 3 days) for 7 weeks; expose the control mice to air at the same time and for the same period."	Ozone, air control	"This study successfully generated a new COPD model by exposing mice to high levels of ozone. This model demonstrated the following: 1) decreased forced expiratory volume 25, 50, and 75/forced vital capacity (FEV25/FVC, FEV50/FVC, and FEV75/FVC), indicating the deterioration of lung function; 2) enlarged lung alveoli, with lung" parenchymal destruction; 3) reduced fatigue time and distance; and 4) increased inflammation"	"Ozone exposure (OE) model is a reliable animal model that is similar to humans because ozone overexposure is one of the etiological factors of COPD. Additionally, it only took 6 - 8 weeks, based on our previous work, to create an OE model, whereas it requires 3 - 12 months to induce the cigarette smoke model, indicating that the OE model might be a good choice for COPD research."
Uh et al. 2015	The Korean journal of internal medicine	Male BALB/c mice, at 7 weeks of age Each group consisted of six animals.	Ozone exposure was performed 2 days after the last day of cigarette smoke inhalation. The ozone system delivered ozone concentrations of 0.1 to 3 ppm, generated by an electric discharge ozone generator (SW-OGMD-L001, Swater Inc., Bucheon, Korea). On the day of the experiment, six mice were placed into the exposure chamber simultaneously and were exposed to 3 ppm for 2 hours. The mice were sacrificed 6 hours after ozone exposure	Mice were divided into the following groups: group I, no smoking and no ozone (NS + NO); group II, no smoking and ozone (NS + O); group III, smoking and no ozone (S + NO); and group IV, smoking and ozone (S + O)	The mean linear intercepts of groups III (S + NO) and IV (S + O) (45 +/- 2 and 44 +/- 3 microm, respectively) were significantly higher than those of groups I (NS + NO) and II (NS + O) (26 +/- 2 and 23 +/- 2 microm, respectively; $p < 0.05$). Fourteen spots that showed significantly different intensities on image analyses of two-dimensional (2D) protein electrophoresis in group I (NS + NO) were identified by LC-MS/MS. The levels of six proteins were higher in group IV (S + O). The levels of "vimentin, lactate dehydrogenase A, and triose phosphate isomerase were decreased by both smoking and ozone treatment in Western blotting and proteomic analyses. In contrast, TBC1 domain family 5 (TBC1D5) and lamin A were increased by both smoking and ozone treatment."	"The levels of vimentin, lactate dehydrogenase A, and triose phosphate isomerase were decreased by both smoking and ozone treatment in Western blotting and proteomic analyses. In contrast, TBC1 domain family 5 (TBC1D5) and lamin A were increased by both smoking and ozone treatment. … TBC1D5 could be a biomarker of ozone-induced lung injury in emphysema."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Fei et al. 2017	Molecular immunology	Pathogen-free, ten-week-old male C57/BL6 mice n = 8–10 for each group	Animals were exposed to ozone produced from an ozoniser (Model 500; Sander Ozoniser, Germany), mixed with air, for 3 h at a concentration of 2.5 parts per million (ppm) in a sealed Perspex container, twice a week for 6 weeks. Control mice were exposed to normal air in corresponding periods.	Mice are divided into 7 parts as follows: air + normal saline, ozone + normal saline, ozone + budesonide (BUD) (0.2 g/L), ozone + low progesterone (0.03 mg/L), ozone + high progesterone (0.3 mg/L), ozone + BUD + low progesterone and ozone + BUD + high progesterone.	Exposure to ozone resulted in a marked lung neutrophilia. Moreover, in ozone-exposed group, the levels of oxidative stress-related interleukin (IL)-1β, IL-6, IL-8, IL-17A, activated NF-κB and p38MAPK, airway inflammatory cells infiltration density, "mean linear intercept (Lm) were greatly increased, FEV25 and glucocorticoids receptors (GR) were markedly decreased. Comparable to BUD, progesterone treatment dose-dependently led to a significant reduction of IL-1β, IL-6, IL-8, IL-17A, activated NF-κB and p38MAPK, and an increase of FEV25 and GR. Progesterone combined with BUD resulted in dramatic changes, compared to monotherapy of BUD or progesterone."	"Progesterone will reduce the chronic airway inflammation exposed to ozone and evaluate whether combination of progesterone with glucocorticoids results in synergistic effects." chronic ozone exposure has profound airway inflammatory effects "counteracted by progesterone and progesterone acts synergistically with glucocorticoids in attenuating the airway inflammation dose-dependently."
Zhang et al. 2018	Molecular immunology	Pathogen-free male C57/BL6 mice, 10 weeks old n=8 for each group	"Mice were exposed to normal air mixed with ozone, which produced by an ozoniser (Model 500; Sander Ozoniser, Germany), for 3 h at a concentration of 2.5 parts per million (ppm) in a sealed Perspex container, twice a week for 6 weeks. … C57/BL6 mice were exposed to ozone for 12 times over 6 weeks, and were administered with progesterone alone or combined with budesonide (BUD) after each exposure until the 10th week."	"Mice were divided randomly into 7 groups as follows: air+sterile saline, ozone+sterile saline, ozone+Budesonide (BUD) (0.2 g/L), ozone+low progesterone (0.03 mg/L), ozone+high progesterone (0.3 mg/L), ozone+BUD+low progesterone and ozone+BUD+high progesterone."	The protein levels of matrix metalloproteinase (MMP)8 and "MMP9 in bronchoalveolar lavage fluid (BALF) and lungs were assessed. Western blot analysis was used to detect the levels of hypoxia-inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF), a-smooth muscle actin (α-SMA), glycogen synthase kinase-3β (GSK-3β). The expression of VEGF and histone deacetylase 2 (HDAC2) in the lung were determined by Immunohistochemical analyses."	Effect of "progesterone on airway remodeling in a murine modeling of exposing to ozone … novel roles of progesterone for the pathogenesis and airway remodeling in COPD. Progesterone plus BUD administration exerts more significant inhibition on airway remodeling with dose-independent. Additionally, progesterone may, to some extent, improve the glucocorticoid insensitivity."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Werthamer et al. 1970	Pathologia et microbiologia	Male Swiss Webster mice weighing approximately 25 g	Exposed to ozone in air from a Caruso electrostatic ozone generator for 2 h sessions every third day for a total period of 75 days ozone concentration was maintained at 4.5 ppm in the exposure cages	Group 1, ozone-desmosterol (100 animals) received daily subcutaneous injections of 0.2 mg desmosterol suspended in 0.2 physiological saline Group 2, ozone-saline (120 animals) received daily subcutaneous injections of the saline vehicle alone Group 3, (55 mice) remained as untreated, unexposed controls	Both groups of mice exposed to ozone with and without desmosterol injections showed inflammatory changes; the significance between the exposed groups and controls exceeded the 99 percentile level. Bronchiectasis and emphysema was almost universally produced. sever brochopneumonia manifesting as microabscesses to necrosis of lobes was relatively common in more severely affected animals. Ozone exposed mice receiving desmosterol in addition, cellular alterations were seen, 38 %. Induction of cellular alterations between ozone exposed mice and unexposed control animals exceeded the 99 percentile level. Differences in epithelial changes between desmosterol-ozone and saline-ozone groups of mice were significant at the 97 percentile confidence level.	Bronchial epithelial alterations and pulmonary neoplasia induced by ozone Desmosterol treatment of the mice appeared to protect somewhat against development of inflammatory responses Cellular architectural changes were observed

Identification		**Population**	**Exposure (ozone)**	**Comparison**	**Results of the study**	**Conclusion of the study**
Li et al. 2013	PLoS One	C57/BL6 mice (Harlan, UK)	Ozone (3 hours; 2.5 ppm) Mice were exposed to ozone (2.5 ppm, 3 hours/12 exposures, over 6 weeks) and studied 24 hours (24h) or 6 weeks (6 wk) late.	Air 6wk, PBS + ozone 6wk, N-acetylcysteine (NAC) + ozone 6wk air 122, ozone 6wk + PBS 6wk, ozone 6w + NAC 6wk	After ozone exposure, there was an increase in functional residual capacity, total lung volume, and lung compliance, and a reduction in the ratio of forced expiratory volume at "25 and 50 milliseconds to forced vital capacity (FEV25/FVC, FEV50/FVC). Mean linear intercept (Lm) and airway hyperresponsiveness (AHR) to acetylcholine increased, and remained unchanged at 6W after cessation of exposure. Preventive NAC reduced the number of BAL macrophages and airway smooth muscle (ASM) mass. Therapeutic NAC reversed AHR, and reduced ASM mass and apoptotic cells."	"Emphysema and lung function changes were irreversible up to 6W after cessation of ozone exposure, and were not reversed by NAC. The beneficial effects of therapeutic NAC may be restricted to the ASM."
Russell et al. 2016	PLoS One	Female BALB/c mice	Female "C57BL/6 mice (Harlan, UK) were exposed to 3ppm of ozone generated from an ozoniser (model 500 Ozoniser, Sander, Germany) for 3 hours, twice a week for 6 weeks. Control groups were exposed to ambient air."	Exposed to cigarette smoke for 75 minutes, twice a day, 5 times week for 6, 8 or 12 weeks using custom-designed, purpose-built nose-only, directed-flow inhalation and smoke exposure systems. Control groups were exposed to ambient air.	Macrophage migration inhibitory factor (MIF) expression correlated with that of hypoxia-inducible factor-1α (HIF-1α)in all patients groups and "in ozone-exposed mice. BAL cell counts, cytokine mRNA and protein expression in lungs and BAL, including MIF, were elevated in ozone-exposed mice and had increased AHR. Dexamethasone had no effect on these parameters in the mouse" but (S,R)3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid methyl ester (ISO-1)attenuated cell recruitment, cytokine release and AHR.	"Repeat ozone challenge evoked reproducible inflammation but attenuated cell damage."

Identification		**Population**	**Exposure (ozone)**	**Comparison**	**Results of the study**	**Conclusion of the study**
Hicks et al. 2010a	Prostaglandins & other lipid mediators	Experiments were performed on 18 male Cynomolgus monkeys (5–7 kg)	One hour post-dose, animals were challenged with ozone (1ppm) for 6h. Six animals were sham exposed to filtered air. "Ozone was generated using two OREC generators (Ozone Research & Equipment Corporation, AZ, U.S.A.) delivered to the inlet of a H2000 whole body exposure chamber. … Monkeys were exposed to a target ozone concentration of 1ppm (or sham exposed to filtered air) for 6h+T90 (time for concentration to reach 90 % of equilibrium, determined in preliminary testing to be 8min) in whole body stainless steel and glass H2000 inhalation chambers. During ozone exposure, monkeys were single housed within wire cages to which they had previously been acclimated." One hour post-ozone exposure, BAL was performed.	"In non-human primates, RO5101576 inhibited allergen and ozone-evoked pulmonary neutrophilia, with comparable efficacy to budesonide (allergic responses). RO5101576 had no effects on LPS-evoked neutrophilia in guinea pigs and cigarette smoke-evoked neutrophilia in mice and rats."	Theses "studies show differential effects of leukotriene B4 (LTB4) receptor antagonism on neutrophil responses in vivo and suggest RO5101576 may represent a potential new treatment for pulmonary neutrophilia in asthma."	Ozone exposure resulted in significant increases in the numbers of neutrophils in the BAL fluid Pre-treatment with RO5101576 (30 mg/kg po) significantly attenuated ozone-evoked increases in the numbers of neutrophils compared to vehicle-treated animals … "differential effects of LTB4 receptor antagonism on neutrophil responses in vivo and suggest RO5101576 may represent a potential new treatment for pulmonary neutrophilia in asthma."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Williams et al. 2009	Pulmonary pharmacology & therapeutics	Pathogen-free, 6–8-week-old male BALB/c mice (Harlan, UK)	Mice were exposed to ozone (3 ppm) or air (control) for 3 h and were studied at 3 h, 20–24 h and 48 h after exposure.	"We used four groups of mice: two groups were exposed to air, dosed with vehicle or Compound A, and two groups were exposed to ozone, dosed with vehicle or Compound A. For each group, mice were studied at 3 h or 20–24 h, following a 3-h exposure to ozone at a concentration of 3 ppm or air. Compound A was administered by gavage (30 mg/kg in 0.2 ml vehicle) or vehicle alone (0.5 % methylcellulose, 0.2 % Tween 80 in PBS), was dosed in the same volume as the active inhibitor. Compound A or vehicle was administered daily for 2 days prior to air or ozone exposure, and 1 h before and 6 h and 16–18 h after exposure to ozone or air."	"Ozone exposure, compared to air exposure increased BAL cathepsin S levels, AHR and BAL inflammatory cells. Compound A (30 mg/kg p.o.) dosing compared to vehicle dosing inhibited ozone-induced AHR (-logPC100 vehicle: -0.70+/-0.12, n=8 vs. cathepsin S inhibitor: -1.30+/-0.06, P < 0.001, n=8) at 20-24 h and BAL neutrophilia at 3 h and 20-24 h (P < 0.05, n=6). Ozone exposure increased levels of BAL cytokines IL-6, TNF-alpha and IFN-gamma. Compound A reduced IL-6 at 3 h and 20-24 h (P < 0.05, n=5) and TNF-alpha, at 20-24 h (P < 0.05, n=6)."	"Ozone exposure increased BAL cathepsin S levels, AHR and BAL inflammatory cells … an important role for cathepsin S in the regulation of ozone-induced AHR and neutrophil cell recruitment and suggest that cathepsin S may be a target in the treatment of oxidative stress-induced AHR and inflammation."

Identification		**Population**	**Exposure (ozone)**	**Comparison**	**Results of the study**	**Conclusion of the study**
Hardaker et al. 2012	Respiratory research	Male and female transient receptor potential melastatin-2 (TRPM2)-deficient mice and their wild type counterparts were backcrossed onto BALB/C	“Unrestrained mice were placed in plastic exposure chamber of the following dimensions: 23 cm wide, 48 cm deep and 17 cm height (0.1 m2) (maximum of 5 mice per chamber) and exposed to 3 parts per million (ppm) ozone or room air for 4 hours. Ozone was generated, at a flow of 480 l/h, and monitored using a computer-controlled ozone simulator system (SIM6050-T; Anseros GmbH, Germany). Animals were killed 3 and 24 hours post exposure.”	“Mice were exposed to ozone (3 ppm for 4 h) or lipopolysaccharide (LPS, 0.3 mg/kg, intranasaly). In another model, mice were exposed to tobacco smoke (750 µg/L total wet particulate matter) for 30 min twice a day on three consecutive days. For the exacerbation model, the smoke exposure on the morning of day 3 animals was replaced with intranasal administration of LPS (0.3 mg/kg). Animals were killed 3 and 24 h after the challenge (ozone and LPS model) or 18 h after the last tobacco smoke exposure.”	“In all models studied, no difference in the bronchoalveolar lavage inflammation could be evidenced when comparing wild type and TRPM2-deficient mice. In addition, no difference could be seen in the lung inflammation as assessed by the measurement of various cytokines/chemokines. Similarly, in various in vitro cellular activation assays using isolated neutrophils and monocytes no significant differences could be observed when comparing wild type and TRPM2-deficient mice.”	“In all the models tested, no difference in the development of airway inflammation or cell activation between TRPM2-deficient mice and their wild type counterparts. These results would suggest that inhibiting TRPM2 activity in COPD would have no anti-inflammatory effect. The results shown that in a mechanistic model of oxidative stress-induced lung injury (ozone exposure) and in several models thought to reproduce aspects of the inflammation observed in COPD, TRPM2-deficiency did not affect the development of airway inflammation. These data suggest that TRPM2 blockers may not have beneficial effects in patients with COPD.”

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Kierstein et al. 2006	Respiratory research	Experiments were performed between 8 and 12 weeks of age	Balb/c and C57BL/6 mice were exposed them to 3.0 ppm ozone for a 2 hrs period. BAL Pulmonary surfactant protein (SP)-D levels, cellular and cytokine content were evaluated 6 hrs later.	“To define the kinetics of the ozone-induced inflammation and SP-D production in more detail, C57BL/6 mice (Jackson Laboratory, Bar Harbor, ME) were exposed to 3.0 “ppm ozone or air for a 2 hrs period and studied 2, 6, 12, 24, 48, and 72 hrs later. Finally, to study the effects of a complete lack of SP-D, SP-D knockout mice were exposed to either 3.0 ppm ozone for 2 hrs or to 0.5 ppm ozone for 24 hrs. BAL was performed 12 hrs (2 hrs exposure) and 24 and 48 hrs (24 hrs exposure) later. In all experiments age- and strain-matched controls were exposed to room air concurrently. The levels and exposure times were based on a previous pilot study (unpublished) and were chosen to accommodate all three different mouse strains and to allow us to study and compare the temporal inflammatory changes. After exposure, groups of mice (n = 6) were euthanized and BAL was performed.”	Ozone-exposed Balb/c mice demonstrated significantly enhanced acute inflammatory changes including recruitment of inflammatory cells and release of KC and IL-12p70 when compared with age- and sex-matched C57BL/6 mice. On the other hand, C57BL/6 mice had significantly higher levels of SP-D and released more IL-10 and IL-6. Increase in SP-D production coincided with the resolution of inflammatory changes. Mice deficient in SP-D had significantly higher numbers of inflammatory cells when compared to controls supporting the notion that SP-D has an anti-inflammatory function in our model of ozone exposure. IL-6, which was highly up-regulated in ozone exposed mice, was capable of inducing the expression of SP-D in vitro in a dose dependent manner.”	“IL-6, which was highly up-regulated in ozone exposed mice, was capable of inducing the expression of SP-D in vitro in a dose dependent manner. … IL-6 contributes to the up-regulation of SP-D after acute ozone exposure and elevation of SP-D in the lung is associated with the resolution of inflammation. Absence or low levels of SP-D predispose to enhanced inflammatory changes following acute oxidative stress.”

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Nambu und Yokoyama 1985	Sangyo igaku. Japanese journal of industrial health	Specific pathogen freem male Wistar strain rats, 6 weeks old	"Pulmonary emphysema was induced in rats by a single intratracheal instillation of swine pancreatic elastase. After adequate development of the pulmonary emphysema, the animals were initially exposed to 1.9 ppm ozone for 3 hrs, and 3 days later, challenge-exposed to 5.1 ppm ozone for 3 hrs and immediately sacrificed to investigate the extent of the development of tolerance to ozone judged by the formation of edema."	Group 1: not exposed to ozone, Group 2: initially exposed to 1.9 ppm ozone for 3hrs alone, Group 3: initially exposed to 1.9ppm ozone and 3 days later challenge-exposed to 5.1ppm ozone for 3hrs, Group 4: challenge-exposed to 5.1ppm ozone for 3hrs alone.	"Although the body weights of the pulmonary emphysematous rats were the same as those of the saline-treated control rats, the lung weights of the former were heavier. The extent of the edema formation by ozone and of the tolerance to ozone of the pulmonary emphysematous rats seemed to be quite similar to those of the saline-treated control rats. On the other hand, although the exposure of the saline-treated control rats to 1.9 ppm ozone for 3 hrs resulted in an increase in lung weight without edema 3 days after the exposure, the pulmonary emphysematous rats did not show such a response."	"The extent of the edema formation by ozone and of the tolerance to ozone of the pulmonary emphysematous rats seemed to be quite similar to those of the saline-treated control rats."

Identification		**Population**	**Exposure (ozone)**	**Comparison**	**Results of the study**	**Conclusion of the study**
Michaudel et al. 2018	Scientific reports	C57BL/6 female mice (Janvier Laboratory, France), 7–8 weeks old	“Mice were exposed to ozone in a plexiglas chamber (EMB 104, EMMS) at 1ppm during 1 h for the acute model, and 1.5 ppm for 2 h, twice weekly during 6 weeks for the chronic model. Ozone is created by ozonisator (Ozonisator Ozoniser S 500 mg, Sander®) and levels was controlled by sensor (ATI 2-wire transmitter, Analytical Technology).”	Air, ozone acute, ozone chronic groups	“Acute ozone exposure caused respiratory epithelial disruption with protein leak and neutrophil recruitment in the broncho-alveolar space, leading to lung inflammation and airway hyperresponsiveness (AHR) to methacholine. All these parameters were increased upon chronic ozone exposure, including collagen deposition. The structure of the airways as assessed by automatic numerical image analysis showed significant differences: While acute ozone exposure increased bronchial and lumen circularity but decreased epithelial thickness and area, chronic ozone exposure revealed epithelial injury with reduced height, distended bronchioles, enlarged alveolar space and increased collagen deposition, indicative of peribronchiolar fibrosis and emphysema as characterized by a significant increase in the density and diameter of airspaces with decreased airspace numbers.”	The structural changes of “the small airways correlated with functional changes allowing to follow the progression from acute to chronic ozone induced respiratory pathology.”
Zychowski et al. 2016	Toxicology and applied pharmacology	C57BL/6 mice (male, 6–8 weeks old at beginning of studies; Harlan Laboratories, Indianapolis, IN)	Mice were subject to acute hypoxia (10.0 % O_2) or normoxia (20.9 % O_2) 24 h a day for 3 wks, followed by a single exposure to ozone. Hypoxia (10 % O_2) was monitored continuously in the exposure chambers and remained at 10 % for 3 weeks.	The initial study involved four treatment groups: normoxia then filtered air (Nx, FA), normoxia then ozone (Nx,ozone), hypoxia then filtered air (Hx,FA), hypoxia then ozone (Hx,ozone). In a second study, fasudil or PBS were intraperitoneally injected at 20 mg/kg at 3 timepoints: once before ozone exposure, once after ozone exposure, and once the following day before euthanasia	Hypoxia significantly increased right ventricular pressure and hypertrophy. ozone exposure in normoxic mice caused lung inflammation but not injury, as indicated by increased cellularity and edema in the lung. However, in hypoxic mice, ozone exposure led to increased inflammation and edema, along with a profound increase in “airway hyperresponsiveness to methacholine. Fasudil administration resulted in reduced ozone-induced lung injury via the enhancement of pulmonary endothelial barrier integrity.”	The hypoxia-induced pulmonary hypertension model led to a clear exacerbation of ozonerelated lung injury, “Increased pulmonary vascular pressure may enhance lung injury, inflammation and edema when exposed to pollutants, and that enhancement of pulmonary endothelial barrier integrity may alleviate such vulnerability.”

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Human exposure study						
Kehrl et al. 1985	The American review of respiratory disease	13 white men with nonreversible COPD (9 current smokers; mean FEV1/FVC, 56 %), America	Randomly exposed on 2 consecutive days for 2 h to air and 0.3 ppm ozone. During exposures, subjects exercised (minute ventilation, 26.4 ± 3.0 L/min) for 7.5 min every 30 min. During exposures, subjects exercised (minute ventilation, 26.4 ± 3.0 L/min) for 7.5 min every 30 min.	Randomly exposed on 2 consecutive days for 2 h to air and 0.3 ppm ozone. During exposures, subjects exercised (minute ventilation, 26.4 ± 3.0 L/min) for 7.5 min every 30 min	On the ozone day the mean airway resistance and specific airway resistance showed the largest (25 and 22 %) changes ($p = 0.086$ and 0.058, respectively). "Arterial oxygen saturation (SaO_2) obtained in 8 subjects during the last exercise interval showed a mean decrement of 0.95 % on the ozone exposure day; this change did not attain significance ($p = 0.074$). Nevertheless, arterial oxygen desaturation may be a true consequence of low-level ozone exposure in this compromised patient group. As normal subjects undergoing exposures to ozone with slightly higher exercise intensities show a threshold for changes in their respiratory mechanics at approximately 0.3 ppm."	Arterial oxygen desaturation may be a true consequence of low-level ozone exposure in this compromised patient group Persons "with COPD are not unduly sensitive to the effects of low-level ozone exposure."
Linn et al. 1983	The American review of respiratory disease	"Twenty-five volunteers with chronic obstructive pulmonary disease of mild to moderately severe degree;" between 45 and 70 yr of age, capable of at least mild brief exercise without supplemental oxygen, and free of medical contraindications to participation (e.g., clinically significant cardiac arrhythmias or acute respiratory infections) during the period of the study, as determined by an initial screening examination. The intended acceptable range of FEV/FVC was 40 to 65 %.	Mean ozone concentration in every exposure study equaled (within 0.01 ppm) the target value of 0.12 ppm. The range of concentrations within any ozone exposure period was 0.10 to 0.14 ppm. No ozone was detectable during control studies.	"Control studied consisted of similar exposures to purified air alone. Control studies were separated from ozone exposures by 1 month, and the order was randomized."	"No significant disturbances in forced expiratory performance or symptoms attributable to O_2 exposure were found. A slight but significant tendency to decreased arterial hemoglobin oxygen saturation (SaO_2) during exercise in ozone was observed. The decrement in SaO_2 with ozone relative to clean air (mean 1.3 %) was near the limit of resolution of the ear oximeter test and was detected by signal averaging."	Arterial hemoglobin oxygen saturation (SaO_2) decreased during exercise in ozone

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Solic et al. 1982	The American review of respiratory disease	Thirteen white men with nonreversible airways obstruction (mean FEV1/FVC, 58 %), of whom 8 were current smokers, U.S.	Randomly exposed for 2 h to air and to 0.2 ppm ozone on 2 consecutive days using a single-blind crossover design. During either exposure, subjects exercised for 7.5 min every 30 min	Randomly exposed for 2 h to air and to 0.2 ppm ozone on 2 consecutive days using a single-blind crossover design	"Measures of respiratory mechanics obtained pre-exposure and postexposure were not significantly affected by either exposure. Similarly, ventilation and gas exchange measured during exercise showed no difference either between exercise periods or exposure days. However, arterial O_2 saturation (SaO_2), measured by ear oximetry during the final exercise period each day was lower (94.8 %) at the end of O2 exposure, than SaO_2 obtained at the end of air exposure (95.3 %), the difference (0.48 %) being significant (p = 0.008)."	"Normal subjects undergoing comparable exposures show a threshold for respiratory mechanical effects at about 0.3 ppm ozone, our data suggest that mild to moderate COPD is not associated with increased sensitivity to low ozone concentrations. However, our data do not rule out the possibility that the response of such subjects might be exaggerated at higher ozone concentrations. … SaO_2 may indicate that indexes of ventilation/perfusion distribution might be more sensitive measures of ozone effect in this compromised patient group than are conventional respiratory mechanics measures."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Gong et al. 1997	Archives of environmental health	Subjects included 9 men who had severe COPD with subnormal carbon monoxide diffusing capacity (i.e., an emphysemic component) and 10 age-matched healthy men, America	Each subject was exposed to 0.24 ppm ozone and to clean air (control) in an environmentally controlled chamber at 24 degrees C and 40 % relative humidity. Exposures were randomized, they occurred 1 wk apart, and they lasted 4 h. During each half-hour interval, light exercise occurred (i.e., average ventilation 20 l/min) for 15 min	Exposed to 0.24 ppm ozone and to clean air (control)	During both control and ozone exposures, group mean symptom intensity and specific airway resistance (SRaw) increased, whereas forced expiratory performance decreased. The healthy subgroup's mean arterial oxygen saturation (SaO2) rose slightly, and the COPD subgroup's mean SaO2 "declined slightly, during exercise. Group mean forced expiratory volume in 1 s (FEV1.0) declined significantly in ozone exposures, compared with controls. Mean excess FEV1.0 loss after 4 h in ozone (relative to control) was 8 % of the preexposure value in the COPD subgroup, compared with 3 % in the healthy subgroup (p > .05 [nonsignificant]). Overall FEV1.0 loss during ozone exposures, including exercise effects, averaged 19 % in the COPD subgroup, compared with 2 % in the healthy subgroup (p < 0.001). Symptoms, SRaw, and SaO2 responses, as well as healthy subjects' postexposure bronchial reactivity, differed little between ozone-exposed and control subjects."	In "older men with or without severe COPD, ozone causes lung dysfunction under "worst-case" ambient exposure conditions, despite older subjects' comparative unresponsiveness to ozone. The combined effect of ozone and exercise on lung dysfunction is markedly greater with COPD. It is still unclear whether COPD causes an increased response to ozone per se."

Identification		**Population**	**Exposure (ozone)**	**Comparison**	**Results of the study**	**Conclusion of the study**
Linn et al. 1983	Archives of environmental health	Twenty-eight volunteers with chronic obstructive pulmonary disease	Exposed to 0.0, 0.18, and 0.25 ppm ozone in purified air for 1hr periods with light intermittent exercise, with exposure conditions presented in random order at 1-month intervals	Exposed to 0.0, 0.18, and 0.25 ppm ozone in purified air for 1hr periods with light intermittent exercise, with exposure conditions presented in random order at 1-month intervals	No statistically significant changes attributable to ozone were found in forced expiratory performance or percent oxyhemoglobin (measured “near the beginning and end of each exposure). No ozone-related changes in clinical status were found by interviews that included the time for 1 wk before to 1 wk after each exposure, except that a moderate increase in lower respiratory symptoms was reported by nonsmokers in 0.18 ppm exposures only.”	“A moderate increase in lower respiratory symptoms was reported by nonsmokers in 0.18 ppm exposures only … A slight decrement in hemoglobin saturation with ozone exposure (reported in two previous studies of chronic obstructive pulmonary disease subjects) may not be a common occurrence under typical ambient exposure conditions.”
Hiltermann et al. 1998	Free radical biology & medicine	Six nonsmoking mild asthmatics responsive to ozone participated in the study, The Netherlands	The study had a double blind, placebo-controlled, cross-over design and consisted of 3 different sessions (with 3 study days each), separated by at least one month. The first session was used to screen the subjects on inclusion criteria. In the other 2 sessions study medication was given. On study day 1 (between 9:00-11:00 a.m.) a baseline FEV1 was measured. This was followed by a methacholine challenge test to obtain a complete dose-response curve to methacholine. On study day 2 (from 2:00-10:00 p.m.) placebo or rALP aerosol was administered at hourly intervals 2 times before and 6 times after ozone exposure. The exposure protocol consisted ofa2h exposure to 0.4 ppm ozone or filtered air with intermittent exercise (20 l/min/m^2 body surface area)	A double blind, placebo-controlled, cross-over design and consisted of 3 different sessions (with 3 study days each), separated by at least one month.	16 h after exposure to ozone, airway hyperresponsiveness to methacholine was increased both “following placebo and rALP treatment. There was no significant difference between placebo and rALP treatment (change in area under the dose-response curve to methacholine: 117.3±59.0 vs 193.6±59.6 % fall x DD; p=.12). Moreover, the immediate decrease in FEV1 after ozone exposure was not significantly different between the two groups (placebo: -29.6±6.7 %; rALP: -20.9±3.8 %; p=.11). In addition, no significant differences were observed in plasma levels of fibrinogen degradation products generated by neutrophil serine proteinases before and after exposure to ozone.”	“Neutrophil-derived serine proteinases are not important mediators for ozone-induced hyperresponsiveness.”

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Johnson 1987	Research report (Health Effects Institute)	Two groups of male human volunteers (non-smokers)	Two groups of male human volunteers (non-smokers) with one receiving 0.5 ppm 0 3 and the other air (controls) were exposed for four hours on two consecutive days in exposure chambers	Two groups of male human volunteers (non-smokers) with one receiving 0.5 ppm 0 3 and the other air (controls)	Examination of blood plasma samples from individuals exposed to 0.5 ppm ozone for four hours on two consecutive days failed to detect any inactivation of alpha-1-proteinase inhibitor "(alpha 1-PI). This result showed that blood alpha 1-PI was not a satisfactory marker for ozone exposure, but, more importantly, demonstrated that inhaling ozone for short periods does not grossly inactivate this important protein. Studies on bronchial leukocyte proteinase inhibitor (BLPI) showed that it is a significant inhibitor of HNE and probably plays a more important role in protecting the lung than previously thought. BLPI, like alpha 1-PI, was found to be inactivated by oxidants, including ozone and NO_2. The mechanism of ozone inactivation of leukocyte proteinase inhibitors was studied using alpha 1-PI, alpha-1-antichymotrypsin (alpha 1-Achy), BLPI, and Eglin C."	Cannot use the specific activity of blood plasma a 1-PI as a marker for ozone exposure BLPI may serve as a marker. ozone and NO_2 will damage a 1 -PI and BLPI. Ozone oxidation of protein amino acids apparently depends on the three dimensional structure of the protein and its amino acid compositions. "It would seem from these results that ozone can damage proteins via the oxidation of any of the following: tryptophan (Trp), methionine (Met), tyrosine (Tyr), or histidine (His) residues."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Biller et al. 2011	Respiratory medicine	Fourteen healthy non-smoking subjects responsive to ozone, Germany Non-smoking was checked by urine cotinine tests. Subjects had to be free of upper or lower respiratory tract infection for at least 4 weeks prior to screening and prior to each visit. Subjects with a positive skin prick test to common aeroallergens were excluded. No regular intake of a prescribed or over-the-counter medication other than paracetamol for pain relief, oral contraceptive medication, hormonal replacement therapy, or dietary and vitamin supplements were allowed.	Subjects were exposed in the Fraunhofer-ITEM exposure chamber to 250 ppb ozone (ozone) and to filtered room air (RA) for 3 h with intermittent bicycle ergometer exercise (15 min exercise alternating with 15 min rest, ventilation rate during exercise adjusted to 20 l/min/m² body surface)	A randomized, double-blind, two-way cross-over study, subjects were exposed to either ozone (ozone) or filtered room air (RA) in an ozone challenge chamber. Subjects were randomized to two different sequences (RA-ozone)/(ozoneRA) in a 1:1 ratio. Exposures were performed at least 14 days apart to avoid carry-over effects.	Significantly increased numbers of sputum and blood neutrophils were observed after ozone, whereas the eNose signals showed no differences between exposures and no correlation with neutrophilic airway inflammation. However, independent of ozone exposure, sensor data correlated with serum SP-D levels and to a smaller extent with blood neutrophil numbers.	Significantly increased numbers of sputum and blood neutrophils were observed after ozone "Exhaled breath profiles as measured by the Cyranose 320 ®did not reflect airway responses to ozone. This suggests that exhaled volatiles did not change with ozone challenges or that the changes were below the detection limits. Conversely, the correlation of eNose signals with blood neutrophils and serum SP-D, i.e. markers of systemic inflammation and lung permeability, suggested that the Cyranose 320® can detect volatile organic compounds of systemic origin."
Cell study						

Identification		**Population**	**Exposure (ozone)**	**Comparison**	**Results of the study**	**Conclusion of the study**
Damera et al. 2009	American Journal of Physiology-Lung Cellular and Molecular Physiology	Airway epithelial cells (NHBE) and smooth muscle cells (ASM) Human ASM cells were isolated from lung transplant donors Frozen NHBE cells were obtained commercially from Lonza	"The ozone exposure incubator for tissue culture was extensively characterized to deliver and maintain ozone concentrations during routine operation. " Ozone exposure at 0.6 ppm for 6 h Exposed to 0.6 ppm of ozone for a period of6hat 37°C in a 5 % CO_2 incubator. The CO_2 -rich incubator. Following ozone exposure, the cultures were reincubated for an additional 18 h in a 5 % CO_2	The ozone exposure incubator for tissue culture was extensively characterized to deliver and maintain ozone concentrations during routine operation	"Air-liquid interface (ALI) cultures of NHBE cells underwent differentiation as determined by mucin secretion, transepithelial electrical resistance (TEER), and ultrastructure parameters. Whereas TNF enhanced basal secretion of IL-6 (57 ±3 %), ozone exposure at 0.6 ppm for 6 h augmented IL-6 levels in basal (41 +/- 3 %) and TNF-(50 ±5 %) primed cocultures compared with that derived from NHBE or ASM monolayers alone. Levels of PGE(2), 6-keto-PGF(1 alpha), PGF(2 alpha), and thromboxane B-2 (TxB(2)) levels in basal and TNF-primed cocultures revealed that ozone selectively enhanced PGE2 production in TNF-(6 ± 3-fold) primed cocultures, with little effect ($P > 0.05$) on diluent-treated cultures. In accordance with ozone-induced increases in PGE2 levels, cyclooxygenase inhibition with indomethacin partially abolished IL-6 secretion. Indomethacin had little effect on constitutive secretion of IL-6 in cocultures, whereas indomethacin completely restored ozone-mediated TEER reduction in TNF- primed cocultures."	Ozone-induced increases in PGE2 levels "ozone selectively enhanced PGE2 production in TNF-(6 ± 3-fold) primed cocultures … A dual role of ozone in modulating IL-6 secretion and TEER outcomes in a PGE(2)-dependent (in presence of TNF stimulus) and -independent manner (in absence of cytokine stimulus)."

Identification		**Population**	**Exposure (ozone)**	**Comparison**	**Results of the study**	**Conclusion of the study**
Li et al. 2018b	Journal of Allergy and Clinical Immunology	Human airway smooth muscle cells (ASMCs)	Exposed to ozone (3 ppm in air) for 3 hours induced pluripotent stem cell–derived mesenchymal stem cells (iPSC-MSCs) 1x10^{6} were intravenously injected 24 hours prior to, or 6 hours after, the exposure.	Groups: ozone saline, ozone MSCs-24hr, ozone MSCs+6hr	iPSC-MSCs attenuated ozone-induced mitochondrial dysfunction, airway hyperresponsiveness, and inflammation in mouse lungs.	iPSC-MSCs offered protection against oxidative stress-induced "mitochondrial dysfunction in human airway smooth muscle cells and in mouse lungs while reducing airway inflammation and hyperresponsiveness. These effects are, at least in part, dependent on cell-cell contact, which allows for mitochondrial transfer, and paracrine regulation. … iPSC-MSCs attenuated ozone-induced mitochondrial dysfunction, airway hyperresponsiveness, and inflammation in mouse lungs."
Clinical trial						
Holz et al. 2015	BMC pharmacology & toxicology	Twenty-four healthy, non-smoking subjects were included, Hannover, Germany The date of the first subject enrolled was the 25th of June 2012, the date of last subject completed was the 30th April 2013.	Subjects were exposed to 250 ppb ozone (ozone) in the Fraunhofer-ITEM exposure chamber under intermittent bicycle ergometer exercise (15 min exercise alternating with 15 min rest, ventilation rate during exercise adjusted to 20 l/min/m^{2} body surface).	In a single-blind, phase 1B proof of concept study, 24 subjects were enrolled to sequentially receive three doses of PUR118 (5.5 mg, n = 18; 11.0 mg, n = 18; 2.8 mg, n = 16). Each dose was inhaled 3 times (1, 13, 25 h, preceded by 2 puffs salbutamol) before the ozone exposure (250 ppb, 3 h intermittent exercise). a single-blind evaluation of PUR118 in five periods separated by at least 2 weeks 'wash-out' to allow the ozone-induced airway inflammation to subside	Sputum neutrophils, sputum CD14+ cells, as well as concentrations of IL1B, IL6, IL8, MMP9, and TNFA in sputum supernatant significantly increased after ozone exposure (n = 24). The percentage of sputum neutrophils (n = 12 who completed all treatments) did not change following treatment with different doses of PUR118. The high dose treatment group (n = 16) showed a decrease in the percentage and number of sputum macrophages ($p \leq 0.05$) as well as "a decrease in blood neutrophils ($p = 0.04$), and an increase in blood CD14 + cells ($p = 0.04$) compared to baseline. All dosages of PUR118 were safe and well tolerated."	"Ozone challenge resulted in the expected and significant increase of sputum inflammatory parameters. Treatment with multiple rising doses of PUR118 was safe and three applications within 25 h prior to the ozone challenge had small effects on ozone-induced airway inflammation."

Identification		**Population**	**Exposure (ozone)**	**Comparison**	**Results of the study**	**Conclusion of the study**
Lazaar et al. 2011	British journal of clinical pharmacology	Subjects were required to have an FEV1 of ≥ 80 % predicted and a documented response to ozone (>10 percentage point increase from baseline) in sputum neutrophils in Germany between October 2007 and July 2008 Twenty-four healthy non-smoking male	Subjects were exposed to 250 ppb ozone over a 3 h period in each of the challenge sessions. During exposure, subjects alternated between 15 min of light exercise on a bicycle ergometer and 15 min of rest.	Ozone challenge study was a randomized, doubleblind, placebo controlled three-way crossover trial randomized to receive a single dose of 50 mg, 150 mg or placebo 1 h prior to ozone challenge	Maximum inhibition (70 %) relative to placebo was observed following administration of SB-656933 400 mg (95 % CI 60 %, 77 %). This was sustained up to a dose of 1100 mg. Single doses of SB-656933 reduced ozone-induced airway inflammation in a dose-dependent manner. Relative to placebo, there were 55 % (95 % CI: 20 %, 75 %) and "74 % (95 % CI 55 %, 85 %) fewer neutrophils in the sputum of subjects after a single dose of 50 mg or 150 mg, respectively. There was a corresponding reduction in myeloperoxidase concentrations in the sputum supernatant of 32.8 % (95 % CI 9.2, 50.3) and 50.5 % (95 % CI 33.3, 63.3)."	"Single doses of SB-656933 reduced ozone-induced airway inflammation in a dose-dependent manner. … SB-656933 is a CXC receptor 2 antagonist that demonstrates dose-dependent effects on neutrophil activation and recruitment within a well-tolerated dose range."
Holz et al. 2010	The European respiratory journal	18 healthy nonsmokers All subjects had a normal airway response to methacholine (provocative concentration that produces a 20 % fall in FEV1 (PC_{20} ≥ 8mg/mL methacholine) within 12 months before the study or at screening. in Germany (approved by the Ethical Committee of the Chamber of Physicians of the State of Schleswig-Holstein, Germany.); from November 2004 to June 2005	"Subjects underwent an ozone challenge test 1 h after the last treatment in each treatment period; during the test, subjects inhaled ozone at 250 ppb for 3 h while exercising at 15-min intervals. "	"A randomised, double-blind, placebo-controlled, three-way crossover study, oral SCH527123 (50 mg once daily, 4 days), prednisolone (50 mg once), or placebo was alternated with 2-week washouts. … Subjects were orally administered each of the following treatments on separate occasions in random order: SCH527123, 50 mg once daily for 4 days and single-dose placebo for prednisolone on day 4; placebo for SCH527123, 50 mg once daily for 4 days and single-dose prednisolone 50 mg on day 4; placebo for SCH527123, 50 mg once daily for 4 days and single-dose placebo for prednisolone on day 4."	"After SCH527123 treatment, the ozone challenge resulted in significantly lower sputum neutrophil counts ($0.13x10^6$/mL) compared with prednisolone ($0.84x10^6$/mL); p<0.001) or placebo ($2.98x10^6$/mL; p<0.001). Comparable results were obtained for total cell count, percentage of sputum neutrophils, and for interleukin-8 and myeloperoxidase in sputum supernatant. Post-challenge, SCH527123 inhibited neutrophilia in peripheral blood but significantly less than in sputum. All treatments were safe and well tolerated."	Ozone-induced neutrophil recruitment "SCH527123 causes significant attenuation of ozone-induced airway neutrophilia in healthy subjects."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Kirsten et al. 2011	Pulmonary pharmacology & therapeutics	18 subjects, two-center (Pulmonary Research Institute, Grosshansdorf, Germany and SCOPE LifeScience, Hamburg, Germany), randomized, double-blind, placebo-controlled, 2-way cross-over study was conducted from September 2009 to December 2009	The subjects inhaled 250 ppb ozone for 3 h, while exercising at 15 min-intervals	"A double-blind, placebo-controlled, randomized, cross-over study Bimosiamose (10 mg bid) was inhaled via a breath actuated nebulizer (AKITA2 APIXNEB®) for 4 days. Treatment was followed by inhalation of ozone (250 ppb) for 3 h with intermittent exercise."	"All treatments were safe and well tolerated. Compared to placebo Bimosiamose reduced the numbers of sputum neutrophils by 40 % (p = 0.068) and concentrations of interleukin-8 and matrix-metalloproteinase-9 in sputum supernatant by 35 % (p = 0.004) and 46 % (p = 0.022), respectively."	"Inhalation of ozone induces an inflammation of the airways, which is dominated by neutrophils." Inhalation of Bimosiamose showed favourable "anti-inflammatory effects on ozone-induced airway inflammation in healthy volunteers."

D Überprüfung der biologischen Plausibilität einer kausalen Assoziation zwischen Ozonexposition und Diabetes in experimentellen Studien durch Systematic Mapping

Identification		**Population**	**Exposure (ozone)**	**Comparison**	**Results of the study**	**Conclusion of the study**
Author	Journal	Description	Description	Description	Outcome	Description
Clinical trial						
Miller et al. 2016a	American journal of respiratory and critical care medicine	A total of 24 volunteers were involved in the study; two clinic visits (n = 24 each) Serum samples for this exploratory study were obtained from Clinical Trial NCT01492517. “A total of 24 volunteers were involved and completed the study. The median age was 27.9 years; there were 20 male and 4 female participants (22 whites, 2 Hispanics). Participants were free of cardiopulmonary diseases and allergies as determined by a detailed medical history questionnaire and physical examination. All subjects were nonsmokers and had normal spirometry. Subjects were informed of the procedures and potential risks and signed an informed consent.”	“During each visit, the subjects were exposed to either 0.3 ppmozone or filtered air for 2 hours in the morning time in a blinded manner. During the exposure, subjects alternated between 15 minutes of rest and 15 minutes of exercise on a cycle ergometer … Ozone was generated by a silent electric discharge method (model 502; Meckenheim, Bonn, Germany). The exposure chambers were maintained at 40 % relative humidity for all exposures.”	A crossover clinical study “The exposure was conducted in a randomized crossover design where two clinical visits of each individual were separated by at least 2 weeks. … Subject was blindly exposed in the morning to either filtered air or 0.3 ppm ozone for 2 hours during 15-minute on-off exercise.”	“Ozone exposure markedly increased serum cortisol and corticosterone together with increases in monoacylglycerol, glycerol, and medium- and long-chain free fatty acids, reflective of lipid mobilization and catabolism. Additionally, ozone exposure increased serum lysolipids, potentially originating from membrane lipid breakdown. Ozone exposure also increased circulating mitochondrial beta-oxidation-derived metabolites, such as acylcarnitines, together with increases in the ketone body 3-hydroxybutyrate.”	“Saturation of beta-oxidation by ozone in exercising humans acute ozone exposure increased stress hormones and globally altered peripheral lipid metabolism in humans, likely through activation of a neurohormonally mediated stress response pathway.”
Animal study						

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Vella et al. 2015	Diabetes	Wistar rats weighing 400–450 g (Janvier SA, Le Genest-Saint-Isle, France) (n = 12, Clean air, n = 12; ozone, n = 12)	“Rats were kept within a Plexiglas hermetic environmental chamber (width 0.35 m, length 0.70 m, height 0.40 m, surface 0.25 m^2, volume 0.1 m^3) supplied with a constant airflow (6 m^3/h) and subjected to 1,570 mg/ m^3 ozone, corresponding to 0.8 ppm for 16 h. Ozone was generated by passing filtered air across a UV light, and concentration inside the cage was controlled by adjusting the inlet flow of air. The ozone concentration was continuously measured using a calibrated UV photometric ozone monitor (range ± 0.001 ppm; catalog #41M; Environement SA, Poissy, France) connected to the outlet line of the chamber. The mean ozone concentration inside the exposure chamber was 0.800 ± 0.05 ppm.	Control “exposure was performed in a similar chamber provided with filtered room air at the same flow rate Some rats were pretreated for 10 days with N-acetylcysteine (NAC) prior to ozone exposure. Rats were given NAC orally in drinking water (10 mmol/L). The water intake was monitored daily to calculate the daily NAC intake. The mean daily intake of NAC was 225 6 10 mg/kg/day. Another independent set of rats was gavaged daily with 4-phenylbutyric acid (PBA; 150 mg/kg) for 4 days prior to ozone exposure.”	“We demonstrated that exposure of rats to ozone induced whole-body insulin resistance and oxidative stress, with associated endoplasmic reticulum (ER) stress, c-Jun N-terminal kinase (JNK) activation, and disruption of insulin signaling in skeletal muscle. Bronchoalveolar lavage fluids from ozone-treated rats reproduced this effect in C2C12 myotubes, suggesting that toxic lung mediators” were responsible for the phenotype. Pretreatment with the chemical chaperone 4-phenylbutyric acid, the JNK inhibitor SP600125, or the antioxidant N-acetylcysteine alleviated insulin resistance, “demonstrating that ozone sequentially triggered oxidative stress, ER stress, and JNK activation” to impair insulin signaling in muscle.	“Ozone plays a causative role in the development of IR and that a realistic, shortterm exposure to ozone causes whole-body insulin resistance that lasts for up to 3 days. This alarming phenotype is due to the production of lung mediators that induce oxidative stress”and the subsequent activation of c-Jun Nterminal kinase (JNK) in skeletal muscle, therefore disrupting insulin-induced signaling and glucose uptake. Ozone pollution could synergize with other dominant factors (obesity and sedentary lifestyle) to accelerate the propensity for Type 2 diabetes and that chaperone molecules or antioxidants could protect susceptible people from complications induced by ozone pollution peaks.

Identification		**Population**	**Exposure (ozone)**	**Comparison**	**Results of the study**	**Conclusion of the study**
Ying et al. 2016	Inhalation toxicology	KKay mice, a genetic diabetic animal model, 4–5 weeks old, Mice (8/group)	"Mice (8/group) were exposed to filtered air (Air), or ozone (ozone; 0.5 ppm) 4 h per day from 8:00 am to 12:00 pm, for 13 consecutive weekdays (5 days/first 2 weeks and 3 days/third week, 4h/day, with no exposures over the intervening weekends).. Ozone-exposed mice received 0.496 ± 0.001 ppm ozone (mean daily concentrations ± standard error of the mean) over the 13 consecutive weekdays. Filtered-air exposed mice received the same exposure regimen, but at ozone chamber concentrations below 0.01 ppm."	"Ozone-exposed mice received 0.496 ± 0.001 ppm ozone (mean daily concentrations ± standard error of the mean) over the 13 consecutive weekdays. Filtered-air exposed mice received the same exposure regimen, but at ozone chamber concentrations below 0.01 ppm."	Ozone exposure increased plasma tnfalpha, as well as expression of vascular cell adhesion molecule (VCAM)-1, inos and IL-6 in both "pulmonary and adipose tissues. Pro-inflammatory CD11b^{+}Gr-1^{lo}7/4^{hi} macrophages were increased by 200 % in adipose tissue, but unchanged in blood. Interestingly, glucose levels were not significantly different in the insulin tolerance test between air- and ozone-exposed mice, whereas fasting insulin levels and Homeostasis model assessment-insulin resistance (HOMA-IR) in ozone-exposed animals were significantly reduced. These changes were accompanied by increased insulin signaling in skeletal muscle and liver, but not adipose tissues. Ozone also caused decrease in body weight and plasma leptin."	In addition to marked local and systemic inflammation, ozone increases insulin sensitivity that may be related to weight loss/leptin sensitization-dependent mechanisms in KKay mice

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Zhong et al. 2016	Inhalation toxicology	Diabetes-prone Japanese KK mice (8/group)	"Mice (8/group) were exposed to filtered air (FA), or ozone (ozone; 0.5 ppm target) for 13 consecutive weekdays (Monday to Friday, 4 h/day) … ozone was generated with an OREC 03V1Clone ozone generator (Ozone Research and Equipment Corp., Phoenix, AZ) using compressed air as a source of oxygen, and monitored with a Dasibi 1003 AH ambient air ozone monitor (Dasibi Environmental Corp., Glendale, CA). The actual chamber concentrations were 0.49586±0.000926 ppm (mean±SEM), and were highly consistent throughout the 13-day study."	Exposed to filtered air (FA), or ozone	"KK mice exposed to ozone displayed an impaired insulin response. Plasma insulin and leptin levels were reduced in ozone-exposed mice. Three-week exposure to ozone induced lung inflammation and increased monocytes/macrophages in both blood and visceral adipose tissue. Inflammatory monocytes/macrophages increased both systemically and locally. CD4 + T cell activation was also enhanced by the exposure of ozone although the relative percentage of CD4 + T cell decreased in blood and adipose tissue. Multiple inflammatory genes including CXCL-11, IFN-gamma, TNFalpha, IL-12, and inos were up-regulated in visceral adipose tissue. Furthermore, the expression of oxidative stress-related genes such as Cox4, Cox5a, Scd1, Nrf1, and Nrf2, increased in visceral adipose tissue of ozone-exposed mice."	"Ozone exposure exacerbates insulin resistance in diabetes-prone mice by triggering oxidative stress and systemic/local inflammatory response."

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Miller et al. 2015	Toxicology and applied pharmacology	Male Wistar Kyoto (WKY) rats Male, 10 weeks old, healthy Wistar Kyoto (WKY) rats (250– 300 g) In the concentration–response study, rats were randomized by body weight into four exposure groups (n = 6/group) to make sure each exposure group had the same overall average body weight. Similarly, in the time-course study, rats were randomized by body weight into six groups (n = 8/group) for two exposure conditions and each time point.”	“Ozone was produced from oxygen by a silent arc discharge generator (OREC, Phoenix, AZ), and its entry into the Rochester style “Hinners” chambers was controlled by mass flow controllers. … WKY rats were exposed to either filtered air (FA) or ozone (0.25, 0.50, or 1.0 ppm), 6 h/day for two consecutive days and sacrificed 18 h after day 2. In the subsequent time-course experiment, three groups of WKY rats were used. 1) The first group was either exposed to FA or 1.0 ppm of ozone for 6 h/day for one day (1 d–0 h), 2) a second group was exposed 6 h/day for two consecutive days (2 d–0h), and 3) a third group was allowed an 18 h recovery, following two consecutive days ofozone exposure (2 d–18 h).”	“WKY rats were exposed to either filtered air (FA) or ozone (0.25, 0.50, or 1.0 ppm), 6 h/day for two consecutive days and sacrificed 18 h after day 2. In the subsequent time-course experiment, three groups of WKY rats were used. 1) The first group was either exposed to FA or 1.0 ppm of ozone for 6 h/day for one day (1 d–0 h), 2) a second group was exposed 6 h/day for two consecutive days (2 d–0h), and 3) a third group was allowed an 18 h recovery, following two consecutive days ofozone exposure (2 d–18 h).”	“Ozone increased serum glucose and leptin on day 1. Glucose intolerance persisted through two days of exposure but reversed 18h-post second exposure. Ozone increased circulating metabolites of glycolysis, long-chain free fatty acids, branched-chain amino acids and cholesterol, while 1,5-anhydroglucitol, bile acids and metabolites of tricarboxylic acid (TCA) cycle were decreased, indicating impaired glycemic control, proteolysis and lipolysis. Liver gene expression increased for markers of glycolysis, TCA cycle and gluconeogenesis, and decreased for markers of steroid and fat biosynthesis. Genes involved in apoptosis and mitochondrial function were also impacted by ozone.”	“Short-term ozone exposure induces global metabolic derangement involving glucose, lipid, and amino acid metabolism, typical of a stress-response.”

Thomson et al. 2016	Toxicological Sciences	Specific pathogen-free male Fischer-344 rats (200–250 g), n=5 for each group	Administered the 11 beta-hydroxylase inhibitor metyrapone (0, 50, 150 mg/kg body weight) and exposed by nose-only inhalation for 4h to air or 0.8ppm ozone. A steady ozone concentration of 0.8ppm (average 0.799 ± 0.033ppm)	“Rats (n=5/group) were administered metyrapone (50, 150 mg/kg; Sigma-Aldrich Canada Co., Oakville, Ontario, Canada) or vehicle (40 % propylene glycol in buffered saline) by subcutaneous injection 1h prior to exposure, a dose-range and time-point shown to block the stress-induced rise in corticosterone, and then exposed for 4h to clean air or to 0.8ppm ozone. A separate group of animals (n=5) was administered corticosterone (10 mg/kg in the same vehicle; Sigma-Aldrich) by subcutaneous injection 1h prior to exposure, and exposed to clean air for 4h. Animals were euthanized immediately after the 4h exposure, along with naive animals (n=5) that remained in cages rather than being introduced into the nose-only exposure system.”	“Ozone inhalation provoked a 2-fold increase in plasma corticosterone, an effect blocked by metyrapone, but did not alter epinephrine levels. Inhibition of corticosterone production was associated with increased inflammatory signaling in the lungs and plasma in response to ozone, consistent with a role for glucocorticoids in limiting local and systemic inflammatory responses. Effects of ozone on insulin and glucagon, but not ghrelin or plasminogen activator inhibitor-1, were modified by metyrapone, revealing glucocorticoid-dependent and -independent effects on circulating metabolic and hemostatic factors. Several immunosuppressive and metabolic impacts of ozone in the lungs, heart, liver, kidney, and spleen were blocked by metyrapone and reproduced through exogenous administration of corticosterone (10 mg/kg body weight), demonstrating glucocorticoid-dependent effects in target tissues. Ozone and metyrapone both significantly decreased plasma glucagon, with the effect of ozone prevented at the high dose of metyrapone. Insulin levels also tended to be lower after ozone exposure (not statistically significant), but were unchanged by ozone at 50 mg/kg metyrapone; insulin	Ozone decreased plasma glucagon and insulin (not significant). Results support involvement of endogenous glucocorticoids in ozone-induced inflammatory and metabolic effects.

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
					levels were significantly decreased at 150 mg/kg metyrapone, with ozone increasing insulin to near control levels.”	
Bass et al. 2013	Toxicology and Applied Pharmacology	Male Brown Norway rats, One, 4, 12, and 24 months old	“A silent arc discharge generator (OREC, Phoenix, AZ) generated ozone from oxygen. Mass flow controllers regulated the entry of ozone into the Rochester style “Hinners” chambers. Photometric ozone analyzers (API Model 400) monitored the ozone concentrations in the chambers. For the acute study, 1, 4, 12 and 24 months old BN rats (n=8–12/age group) were exposed for 6 h/day on 2 consecutive days to either FA (0 ppm) or ozone (0.25 ppm and 1.0 ppm).” For the subchronic study, 1, 9 and 21month old BN rats (n=8–12/age group) were exposed to FA or ozone (0.25 or 1.0ppm) for 6 h/day × 2 days/week over a 13week period (referred to here by their ages at the end of the 13 week period: 4, 12, and 24 months). For the time-course study, 4 month old BN rats (n =6) were exposed to FA or 1.0 ppm ozone 6 h/day for 1 day or for two consecutive days.One group of rats was allowed to recover for 18h after 2 days of ozone exposure.	“One, 4, 12, and 24-month-old Brown Norway (BN) rats were exposed to air or ozone, 0.25 or 1.0 ppm, 6 h/day for 2 days (acute) or 2 d/week for 13 weeks (subchronic). Additionally, 4month old rats were exposed to air or 1.0 ppm ozone, 6 h/day for 1 or 2 days (time-course).”	“Acute ozone caused hyperglycemia and glucose intolerance in rats of all ages. Ozone-induced glucose intolerance was reduced in rats exposed for 13 weeks. Acute, but not subchronic ozone increased alpha(2)-macroglobulin, adiponectin and osteopontin. Time-course analysis indicated glucose intolerance at days 1 and 2 (2N1), and a recovery 18 h post ozone. Leptin increased day 1 and epinephrine at all times after ozone. Ozone tended to decrease phosphorylated insulin receptor substrate-1 in liver and adipose tissues. Endoplasmic reticulum (ER) stress appeared to be the consequence of ozone induced acute metabolic impairment since transcriptional markers of ER stress increased only after 2 days of ozone.”	Ozone exposure produced profound metabolic effects in rats of all ages characterized by acute hyperglycemia, impaired glucose tolerance, and increased circulating leptin, but not the pro-inflammatory cytokine, IL-6. These effects accompanied a trend of decreased insulin as well as liver and adipose phospho insulin receptor substrate-1 (IRS-1), suggesting modest insulin insensitivity. The time-course study showed marked increases in circulating epinephrine at all times suggesting the contribution of sympathetic neurohormonal activation. Acute ozone exposure induces marked systemic metabolic impairments in BN rats of all ages, likely through sympathetic stimulation.

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Miller et al. 2016b	Toxicology and Applied Pharmacology	Heathy male Wistar Kyoto (WKY) rats (250–300 g)	“Ozone was generated from oxygen by a silent arc discharge generator (OREC, Phoenix, AZ) and its entry into the Rochester style “Hinners” chambers was controlled by mass flow controllers. Male Wistar Kyoto rats were exposed to air or 0.25 ppm or 1.00 ppm ozone, 5 h/day, 3 consecutive days/week (wk) for 13 wks, markers were determined immediately after 13 wk or following a 1 wk recovery period (13 wk + 1 wk recovery).”	“Animals underwent whole body exposure to 1) filtered air, 2) 0.25 ppm ozone, or 3) 1.0 ppm ozone for 5 h/day, 3 consecutive days/ wk for 13wks. Animals were divided into two cohorts: cohort 1 and cohort 2. For cohort 1, necropsies were performed immediately post final exposure (13 wk). For cohort 2, necropsies were performed after 1 wk recovery in their home cages following the 13 wk exposure (13 wk + 1 wk recovery) to determine if ozone effects were reversible.”	“Episodic ozone exposure is associated with persistent pulmonary injury and inflammation, fasting hyperglycemia, glucose intolerance, as well as, elevated circulating adrenaline and cholesterol when measured at 13 wk, however, these responses were largely reversible following a 1 wk recovery. Moreover, the increases noted acutely after ozone exposure in non-esterified fatty acids and branched chain amino acid levels were not apparent following a subchronic exposure. Neither peripheral or tissue specific insulin resistance nor increased hepatic gluconeogenesis were present after subchronic ozone exposure. Instead, long-term ozone exposure lowered circulating insulin and severely impaired glucose-stimulated beta-cell insulin secretion.”	“We demonstrate that subchronic weekly episodic ozone exposure induces persistent pulmonary injury/inflammation, hyperglycemia, glucose intolerance, and increases in cholesterols. We further show that while peripheral insulin resistance did not occur by subchronic episodic ozone exposure, it had a major impact on β-cell insulin secretion in response to circulating glucose, likelymediated by increased circulating adrenaline levels. This, together with reduced circulating insulin levels after subchronic ozone exposure, supports a link between chronic ozone exposure and type 1 diabetes.”

Identification		Population	Exposure (ozone)	Comparison	Results of the study	Conclusion of the study
Thomson et al. 2018	Toxicology and Applied Pharmacology	Specific pathogen-free male Fischer-344 rats (200–250 g)	“One hour prior to ozone exposure, rats were administered vehicle (40 % propylene glycol in buffered saline), 50 mg/kg body weight metyrapone, or 10 mg/kg body weight corticosterone by subcutaneous injecti. Inhalation exposures were conducted using clean air or 0.8 ppm ozone for 4 h in whole body chambers (n=8/group with the exception of corticosterone group exposed to air where n=6). A silent arc generator (Erwin Sander, Uetze, Germany) made ozone from medical-grade oxygen. A feedback loop maintained a steady ozone concentration of 0.8 ppm (average 0.791 ppm) by measuring the ozone concentration (TECO model 49; CD Nova-Tech, Markham, Ontario) in the centre of the chamber and adjusting the ozone bypass flow mixing with the main airstream (400 lpm High-efficiency particulate air, HEPA-filtered air). … Male Fischer-344 rats were exposed to clean air or 0.8 ppm ozone for 4 h.”	“Hypothalamic-pituitary-adrenal (HPA) axis involvement in ozone effects was tested through subcutaneous administration of the glucocorticoid synthesis inhibitor metyrapone (50 mg/kg body weight), corticosterone (10 mg/kg body weight), or vehicle (40 % propylene glycol) prior to exposure. A glucose tolerance test (2 g/kg body weight glucose) was conducted immediately after exposure, with blood samples collected at 0, 30, 60, 90, and 120 min.”	“Ozone exposure impaired glucose tolerance, an effect accompanied by increased plasma triglycerides but no impairment of insulin release. Ozone diminished glucagon, Glucagon-like Peptide 1 (GLP-1), and ghrelin responses to glucose, but did not significantly impact inflammatory/endothelial analytes. Metyrapone reduced corticosterone but increased glucose and triglycerides, complicating evaluation of the impact of glucocorticoid inhibition. However, administration of corticosterone reproduced the profile of ozone effects, supporting a role for the HPA axis. The results show that ozone-dependent changes in glucose tolerance are accompanied by altered metabolic and endocrine responses to glucose challenge that are reproduced by exogenous stress hormone.”	“Ozone alters the metabolic and endocrine response to glucose challenge.”

E Einwohnendenzahlen in den SOMO35-Konzentrationsklassen in 500 µg/m^3-Schritten für den Zeitraum 2007 bis 2016

Konzentrationsklasse	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
<=1000	154342	23636	33041	33997	36121	18330	8867	15596	2373	7477
<=1500	885136	513746	190009	156147	178878	636015	40045	518475	76435	28867
<=2000	2493146	1532546	1519245	704580	1025431	6603713	1434737	6036454	791636	1929243
<=2500	8578976	6457696	8501578	4481291	4249102	14127271	8612165	13436710	4877437	11320826
<=3000	15415694	13957575	18403632	14974511	9471720	13934129	18099943	15247477	11077802	19978266
<=3500	15986985	18580108	20787245	22320364	15906899	13441035	20393420	16357701	13017662	17805951
<=4000	16470417	17934122	16179128	17596415	19483045	13644740	17245823	13909185	8996015	14647488
<=4500	11683506	11686890	9229460	12552786	16489463	9964617	9696751	9337310	9683416	9737670
<=5000	5353977	5992347	3847047	5006316	9122322	4828631	3399184	4001709	13808571	3697024
<=5500	1947895	2435536	1166096	1608945	2841487	2122923	995726	1040435	10019593	816624
<=6000	754644	1052846	284386	611879	979406	629244	207560	171558	5760536	193155
<=6500	311626	139516	72511	172169	309394	131670	96402	170004	1483516	81319
<=7000	66741	8629	65425	21834	134328	142705	41540	34162	418471	46055
<=7500	130238	6292	30004	20007	28879	54320	20010	18287	95444	23611
<=8000	77321	1809	6659	24888	30189	29639	18602	15627	86199	8867
>8000	13638	988	8816	38153	37618	15300	13507	13592	129176	1836

Abkürzungen: µg/m^3, Mikrogramm pro Kubikmeter

Quelle: Eigene Darstellung der vom UBA bereitgestellten Daten und Daten des Zensus 2011(Statistische Ämter des Bundes und der Länder 2018)

F Einwohnendenzahlen in den Sommer-Ozonkonzentrationsklassen in 2 µg/m³-Schritten für den Zeitraum 2007 bis 2016

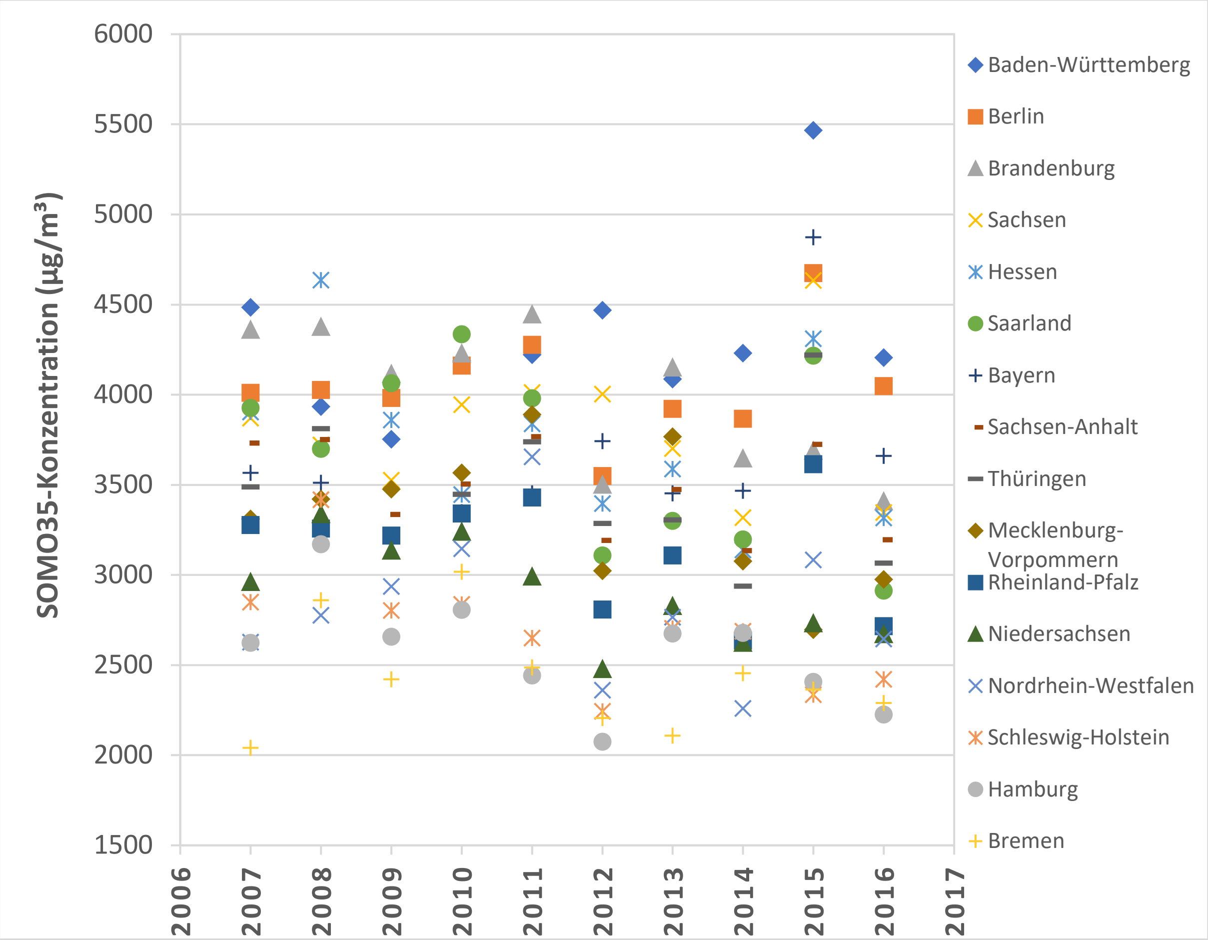
Konzentrations-klasse	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
<=65	886325	310313	56653	81148	33815	38882	15221	150952	1441	8881
<=67	365843	307411	35488	96786	32016	159671	24963	212403	7421	3115
<=69	781323	493751	184239	194352	43074	397974	151062	586399	951	103766
<=71	1572423	931570	334847	400513	160427	1136720	547480	1403883	18227	256650
<=73	2604448	1881790	732975	816402	415149	2103290	1768268	2480359	93279	1055652
<=75	3940601	3008342	1581380	2130202	1034913	3879149	3513101	4293854	381876	2309208
<=77	6078470	4756897	3144965	3704829	2369018	6350297	5959323	5744890	1431507	4941603
<=79	7482862	6371071	5758476	6362753	3725111	7056953	9187367	6798004	3919525	8495963
<=81	8062195	8326015	9394304	10122515	5484437	7378463	11158723	8045378	6311246	8604301
<=83	9526449	10200112	11266979	12201498	8079974	8285058	11771977	9465496	8529297	8663139
<=85	10281023	12076965	11774249	12211288	10886650	8230954	11784145	11859099	7892481	9813692
<=87	9942446	10611827	11645262	11671423	12398381	8384515	10806744	10536228	5963315	9611919
<=89	8130091	8127799	9438555	9195801	12531396	9548872	7313887	8161170	5434616	10149988
<=91	5164494	6204592	6846496	5769922	10697177	7516552	3415997	6137671	6613118	8102940
<=93	2580387	3303067	4473919	2932698	6983428	4855449	1718436	2695695	8834962	4920336
<=95	1391891	1756662	2178889	1368145	3093608	2551361	772161	1051442	8512339	2147546

Konzentrations-klasse	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
<=97	780596	1149052	953089	594766	1263112	1417679	160828	420266	7022794	705814
<=99	330495	442987	297734	278231	643635	604435	66342	169096	5057355	274210
<=101	166833	49660	106953	89546	258566	189657	98929	54109	2731857	84151
<=103	74887	8545	61409	20020	100752	137411	39172	23081	870314	42262
<=105	156126	2748	40744	18403	22172	54154	19489	18980	356372	25660
>105	24074	3106	16677	63041	67471	46786	30667	15827	339989	3486

Abkürzungen: µg/m³, Mikrogramm pro Kubikmeter

Quelle: Eigene Darstellung der vom UBA bereitgestellten Daten und Daten des Zensus 2011 (Statistische Ämter des Bundes und der Länder 2018)

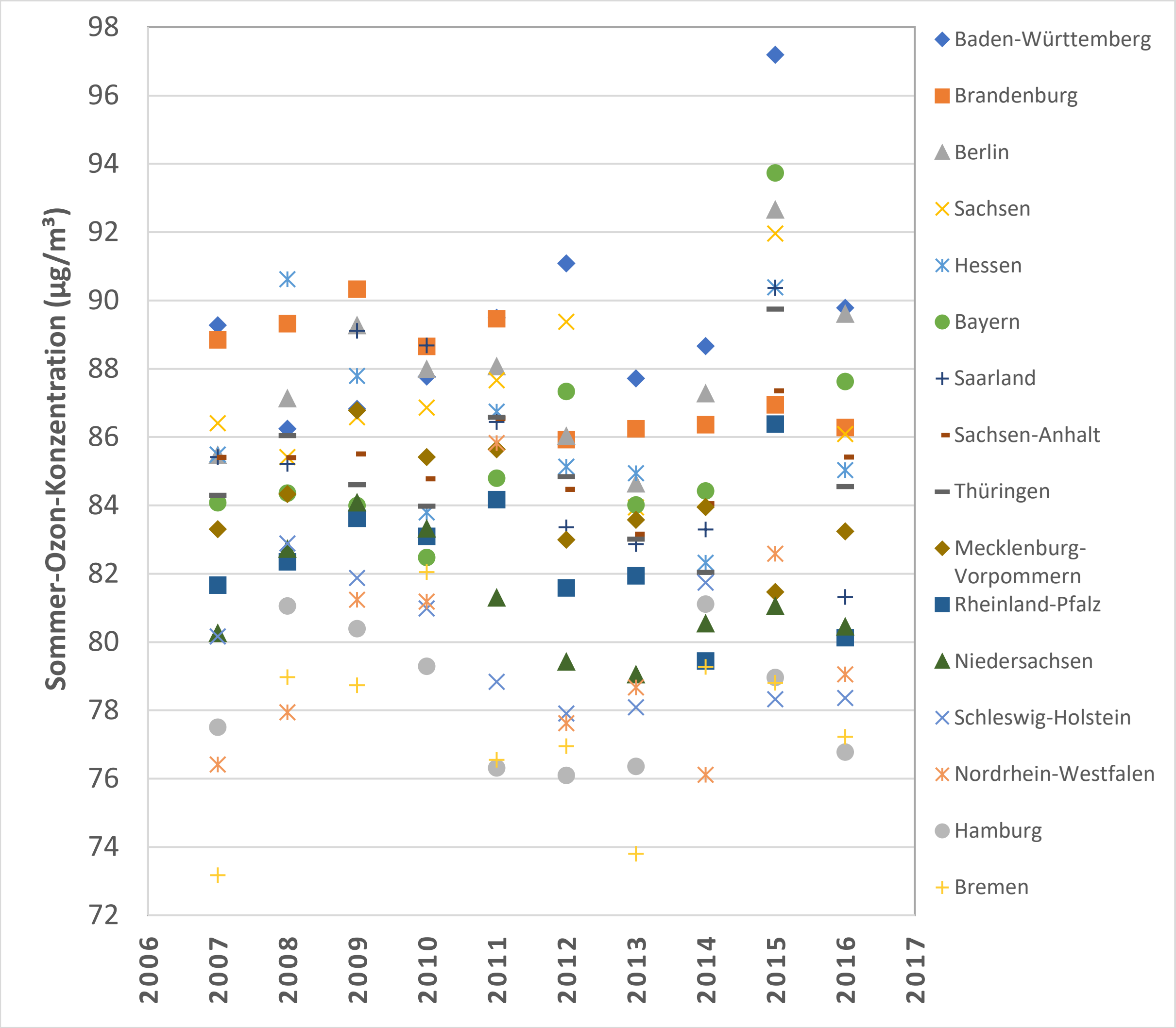
G Flächengemittelte SOMO35-Konzentration für die jeweiligen Bundesländer für den Zeitraum 2007 bis 2016



Abkürzungen: µg/m³, Mikrogramm pro Kubikmeter; SOMO35, Summe der Ozonmittelwerte über 35 ppb basierend auf den Messungen der Hintergrundstationen; ppb, parts per billion

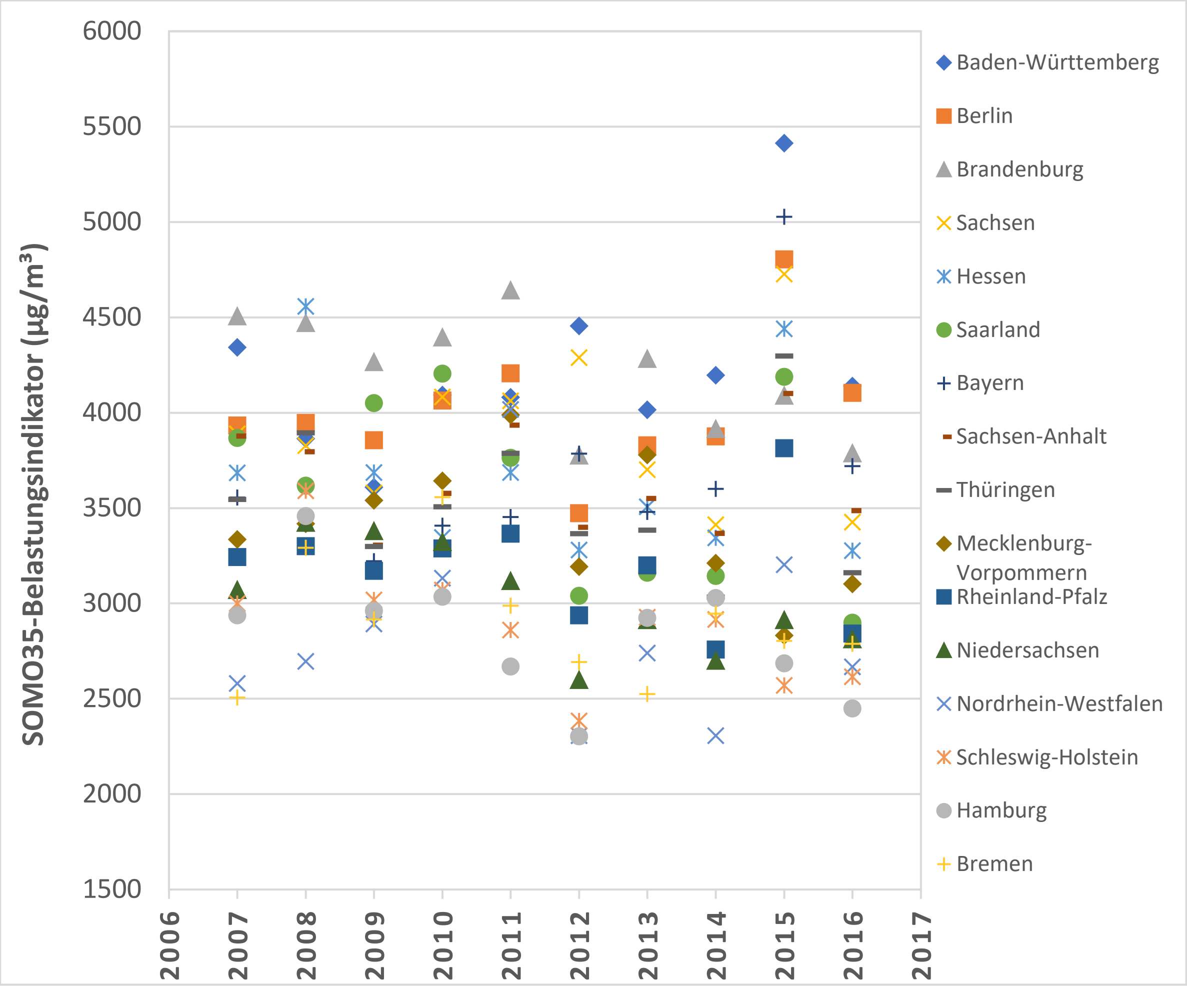
Quelle: Eigene Darstellung auf Basis der vom UBA bereitgestellten Daten

H Flächengemittelte Sommer-Ozon-Konzentration für die jeweiligen Bundesländer für den Zeitraum 2007 bis 2016



Abkürzungen: µg/m³, Mikrogramm pro Kubikmeter
Quelle: Eigene Darstellung auf Basis der vom UBA bereitgestellten Daten

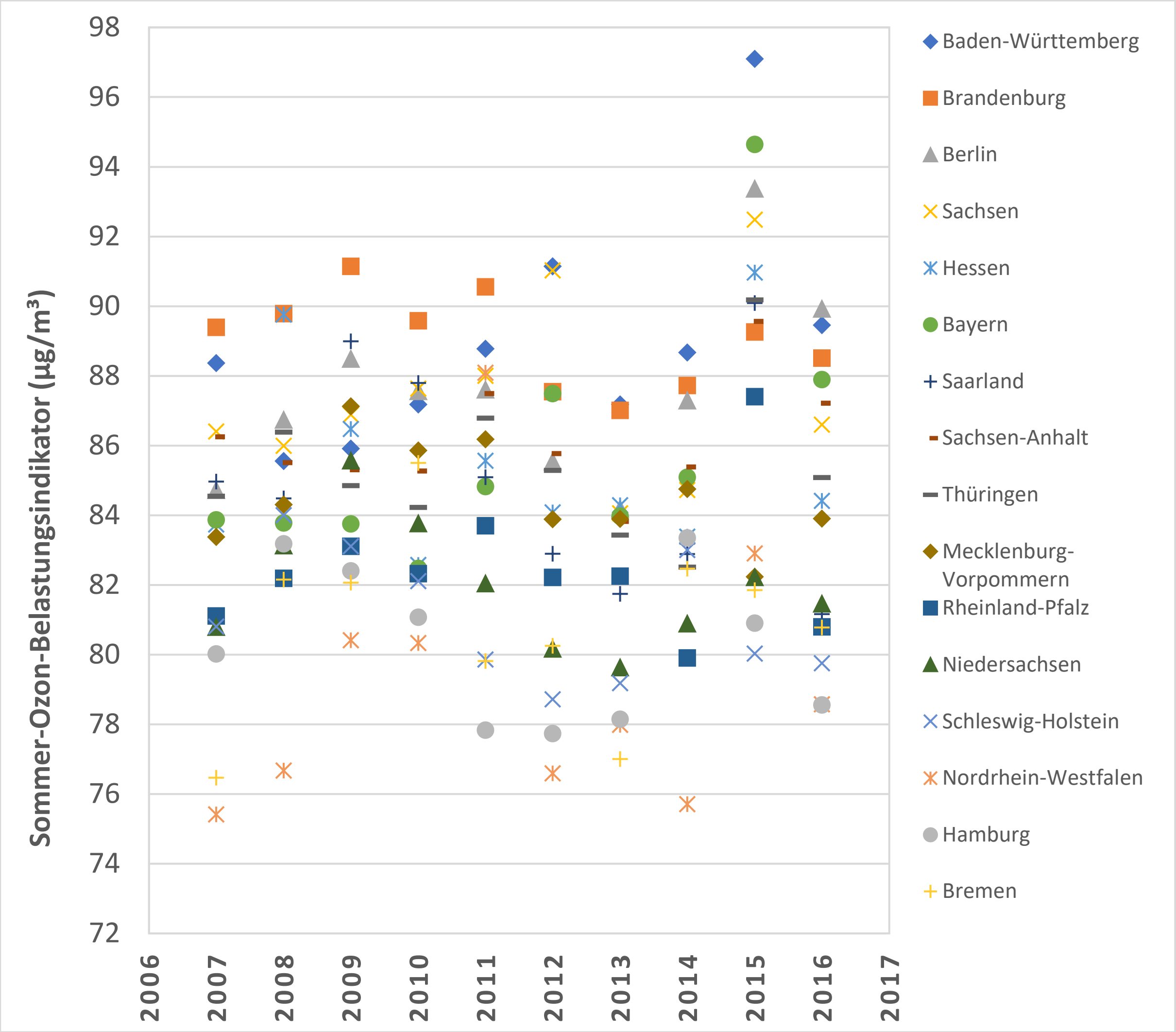
I SOMO35-Belastungsindikator für die jeweiligen Bundesländer für den Zeitraum 2007 bis 2016



Abkürzungen: µg/m³, Mikrogramm pro Kubikmeter; SOMO35, Summe der Ozonmittelwerte über 35 ppb basierend auf den Messungen der Hintergrundstationen

Quelle: Eigene Darstellung auf Basis der vom UBA bereitgestellten Daten

J Sommer-Ozon-Belastungsindikator für die jeweiligen Bundesländer für den Zeitraum 2007 bis 2016



Abkürzungen: µg/m³, Mikrogramm pro Kubikmeter

Quelle: Eigene Darstellung auf Basis der vom UBA bereitgestellten Daten