

The Health Impact of Air Pollution

An expert report of the International Society for Environmental Epidemiology (ISEE) and the European Respiratory Society (ERS)

Prof Dr Annette Peters, MSc, Helmholtz Centre of Munich
and Ludwig-Maximilian University of Munich, ISEE President
in 2012-2013, ISEE Policy Committee member

Prof Dr Barbara Hoffmann, MD, MPH, University Düsseldorf, Chair
of the Environment and Health Committee of the ERS, Chair of ISEE
Europe 2015-2017

Prof Dr Bert Brunekreef, University of Utrecht, Netherlands,
ISEE President in 2000-2001, Chair of the Environment and Health
Committee of the ERS (2014-2017)

Prof Dr PhD Nino Künzli, MD, Swiss Tropical and Public Health
Institute (Swiss TPH), Basel, and University of Basel, Switzerland

Meltem Kutlar Joss, MSc ETH, MPH, Swiss Tropical and Public
Health Institute (Swiss TPH), Basel, Switzerland

PProf Dr PhD Nicole Probst-Hensch, Swiss Tropical and Public
Health Institute (Swiss TPH), Basel, and University of Basel

Prof Dr PhD Beate Ritz, MD, University of California, Los Angeles,
USA, ISEE President

Prof Dr Holger Schulz, MD, Helmholtz Centre of Munich

PD Dr Kurt Straif, MD, MPH, PhD, Lyon, France

Prof Dr Dr H. Erich Wichmann, MD, formerly Helmholtz Centre of
Munich and Ludwig-Maximilian University of Munich

Abstract

The air pollutants particulate matter, ozone and nitrogen dioxide affect the health of populations in Germany, as well as in Europe. The effects start in the lung, but air pollution has impacts on the entire body. In 2005, the World Health Organisation (WHO) revised the 2005 global Air Quality Guidelines for particulate matter, ozone and nitrogen dioxide [1], recommending values that are exceeded in many places in Germany [2]. Those pollutants have been proven to reduce life expectancy and induce respiratory and cardiovascular diseases [3]. Since 2005, scientific evidence showing health effects of all three pollutants has increased substantially. The carcinogenic effect of particulate matter is now considered to be proven [4]. Furthermore, adverse effects on foetal development during pregnancy [5, 6, 7], lung and brain development in children [8, 9], diabetes [10, 11] and dementia [12] have been shown. Importantly, recent studies have documented that adverse effects can be observed at concentrations below the current WHO guideline values [13-15]. In particular, the EU standard for particulate matter smaller than 2.5 μm (PM_{2.5}) should be lowered considerably and brought into line with the recommendations of the World Health Organisation.

What are the air pollutants particulate matter, ozone and nitrogen oxides?

Particulate matter consists of particles less than 10 micrometres in size. It has many sources [16]: particulate matter is generated by motor vehicles, power plants, home furnaces and heaters as well as industrial facilities that directly release such particles. In addition, these sources emit the gaseous pollutants sulphur dioxide and nitrogen oxides that, along with ammonia emissions from agriculture, contribute to the formation of particulate matter in the atmosphere and thereby to pollution [17]. Particulate matter can also arise from natural sources, for example by soil erosion or particles that originate from plants and microorganisms..

Ozone is formed close to the ground from pollutant precursors, mainly nitrogen oxides and volatile organic compounds, through photochemical processes by intense solar radiation [18].

Nitrogen oxides (nitrogen monoxide and nitrogen dioxide) are released during combustion processes. The main sources of nitrogen oxides are internal combustion engines and coal, oil, gas, wood and waste incinerators. In urban areas, road traffic is the main source [19]. Nitrogen oxides are also major precursors of ozone and contribute to the formation of particulate matter.

How do the air pollutants particulate matter, ozone and nitrogen dioxide affect the lung?

Particulate matter is inhaled into the lung through airways. In particular, particulate matter smaller than 2.5 µm (PM_{2.5}) is able to get into the smallest airways and pulmonary alveoli. Ultrafine particles under 100 nanometres in size may also enter the blood circulation and thereby reach other organs. The adverse health effects of the particles are due to a wide variety of chemical and physical properties which mainly cause oxidative stress and inflammatory reactions throughout the body [20]. The particles that we inhale are always a mixture from many sources. Experimental studies have identified particles from combustion processes as especially hazardous to health [21].

Ozone and nitrogen dioxide are irritant gases and have oxidation capacity. They penetrate deeply into the lung, cause oxidative stress [22], provoke inflammatory reactions and interact with pulmonary wall structures. Nitrogen monoxide on the other hand, a substance that is also produced by the body itself, is harmless to the human body [23].

How are the effects of air pollutants investigated in scientific studies?

Experiments on cells and on animals, controlled exposure of volunteers to pollutants and epidemiological studies contribute to the overall scientific evidence on health effects of air pollutants. In total, more than 71,000 studies are currently available in the medical literature. The primary purpose of experimental studies is to examine the adverse effects of air pollutants on health due to their chemical and physical properties and to understand the mechanisms by which they interact with cells and organs. Human

exposure studies investigate short-term effects. Large-scale epidemiological observation studies are the method of choice for assessing the long-term effects on public health. Large cohort studies are especially worth mentioning in this regard, as they are able to include children or patients with health problems.

What diseases are caused by air pollutants?

Particulate matter can cause respiratory diseases and cardiovascular disorders, resulting in lower life-expectancies [24, 25]. The effects range from short-term health effects such as hospital admissions, and ultimately to death. Such effects may occur acutely in response to high concentrations of particulate matter or as consequences of long-term exposure [cf. 3]. The evidence for lung cancer and cardiovascular diseases is now recognised as “causal”, and the evidence for other respiratory diseases as “probably causal” [26]. In addition, it is probable that air pollution exposure has effects on the whole body [5], especially on foetal development during pregnancy [6, 7], lung and brain development in children [8, 9], diabetes [11] and dementia [12].

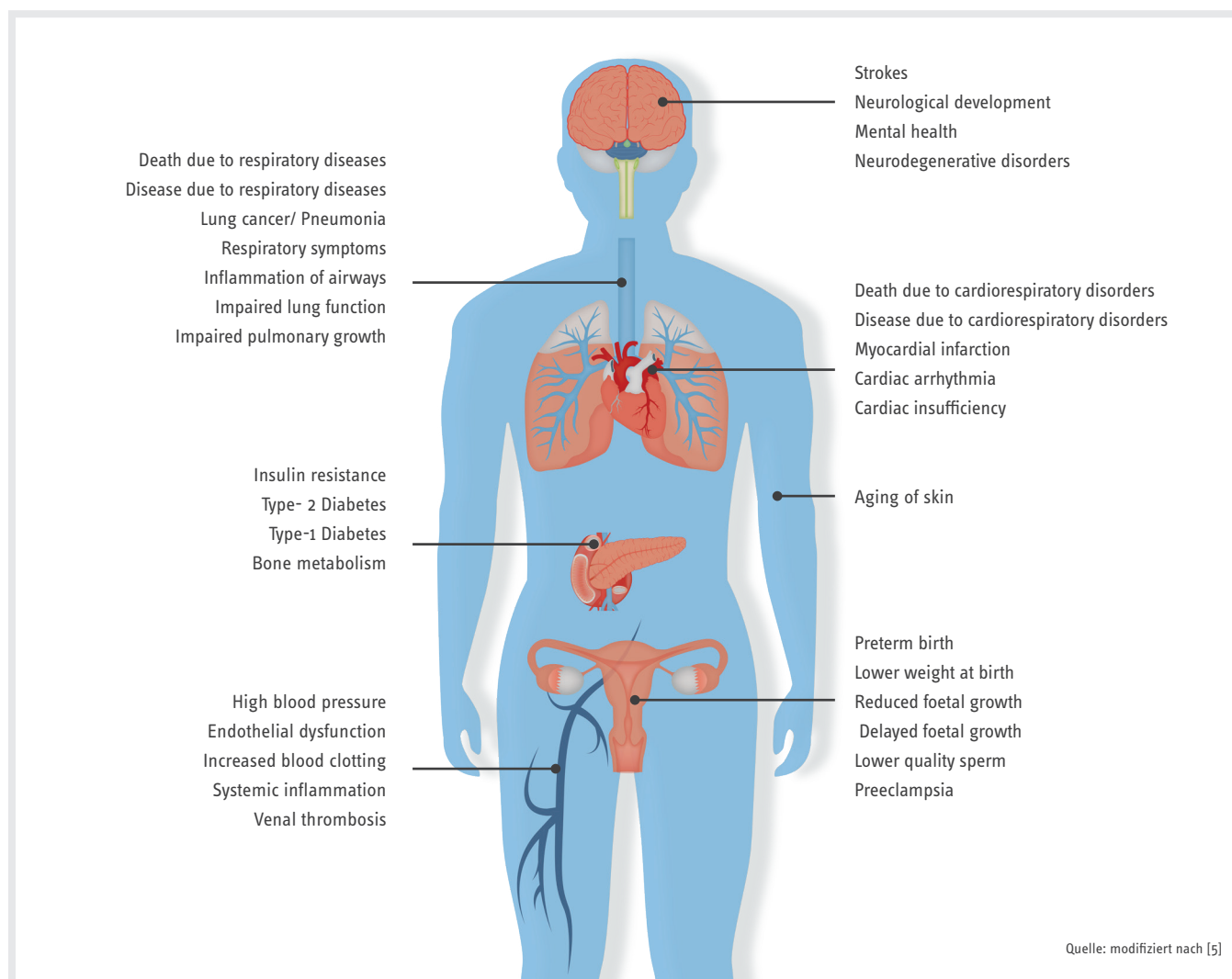
Ozone leads, in the short-term, to increased mortality due to respiratory diseases and to increases in respiratory-related emergency treatment and hospitalization, effects which are classified as “causal” [27]. Short-term ozone exposure is classified as “probably causal” with respect to the increase in the overall mortality and cardiovascular mortality. Long-term exposure to ozone pollution is correlated with increased respiratory-related mortality, an increased number of asthma cases and exacerbated symptoms among asthma-patients, which is also classified as “probably causal” [27].

Nitrogen dioxide leads to exacerbation of health problems among asthmatics and is classified as causal [28, 29]. It has been classified as “probably causal” for the occurrence of other respiratory diseases [29]. Recent studies [30-34] and a systematic review [35] also indicate an association with cardiovascular diseases [30-35] and diabetes [35].

The table summarises these established relationships, which are based on published assessments up to 2016. Relationships are considered to have been proven to be causal if sufficient studies are available that 1) rule out the influence of random associations, biases and other confounding factors, and 2) are based on environmentally relevant concentrations of pollutants. In general, relationships can be substantiated by observational studies as well as experimental studies. “Probably causal” refers to correlations where there are clear indications of a causal link but the current data are insufficient to satisfy all criteria of causality.

Pollutant	Effects on health	Assessment	Source
Particulate Matter (<2.5µm)	Death	causal	[26]
	Cardiovascular diseases	causal	[26]
	Lung cancer	causal	[4]
	Respiratory diseases	probably causal	[26]
Ozone	Short-term effects on respiratory diseases	causal	[27]
	Short-term effects on cardiovascular diseases	probably causal	[27]
	Respiratory diseases	probably causal	[27]
Nitrogen dioxide	Short-term effects on respiratory diseases	causal	[29]
	Respiratory diseases	probably causal	[29]

It should be noted, however, that the established causal effects constitute only part of the effects on health. The figure below (adapted from [5]) gives an overview of the effects on the whole body observed in population-based studies.



Symptoms resulting from exposure to air pollution cannot be clinically distinguished from the same symptoms that may have resulted from other causes. In practice, a physician cannot usually identify the immediate cause of a heart attack or of an asthma attack because there are often many different contributing causal factors.

Are the effects of air pollutants independent from one another?

The regulated air pollutants particulate matter, ozone and nitrogen dioxide have common sources, and often occur at the same time and place, and this affects the human body in combination [36]. Further, there are additional air pollutants, such as soot, ultrafine particles, tiny particles of just a few nanometres, or organic carbohydrates that may be present together with the particulate matter and nitrogen dioxide [3]. Particularly in the case of nitrogen dioxide, it is controversial whether the long-term effects are attributable to nitrogen dioxide alone or rather to a mixture of pollutants for which nitrogen dioxide is an indicator [3]. There is an urgent need for research to disentangle the contribution of correlated air pollutants, especially for soot and ultrafine particles [3].

How are the recommendations for guideline values derived?

International expert committees regularly summarise the available scientific literature. The scientific evidence is discussed intensively and evaluated according to systematic, transparent and reproducible criteria. The summaries are reviewed by third parties. The 2005 recommendation of the World Health Organisation (WHO) was based on the available studies at the time. It was particularly challenging to derive a target value for particulate matter and nitrogen dioxide because the epidemiological studies gave no indications of threshold values below which no adverse effects on health are expected [1]. The recommended target value of $40 \mu\text{g}/\text{m}^3$ for nitrogen dioxide was determined on the basis of long-term animal experiments and population-based studies [1].

The appearance of many new scientific findings led the European Union to commission two technical reports in 2013, in which an updated analysis of the evidence for the WHO recommendations was conducted. These reports indicated that statistically significant effects on health were observed at nitrogen dioxide concentrations as low as $20 \mu\text{g}/\text{m}^3$ [3, 37], based primarily on a meta-analysis of more than 15 long-term nitrogen dioxide studies [25]. A comprehensive review of the 2005 recommendations based on the 2013 assessment [3] and additional scientific findings since then is currently in progress under the direction of the WHO.

How do recommendations become standards?

The definition of standards is a political process that takes scientific recommendations into consideration, including those of the WHO. In the European Union, the standards are adopted by the EU Parliament and incorporated into national law by means of implementation provisions. The European Union relies partially on the WHO recommendations. For example, in 2008 the WHO standard for nitrogen dioxide. In the case of particulate matter, a significantly less protective value of $25 \mu\text{g}/\text{m}^3$ was implemented, instead of the WHO recommended value of $10 \mu\text{g}/\text{m}^3$ for $\text{PM}_{2.5}$.

United States legislation is derived from periodically updated scientific assessments required by law [26, 27, 29]. Overall, these region-specific procedures result in differences in legislation worldwide [38]. Europe urgently needs to reduce the standards on particulate matter in accordance with the latest scientific findings. In Switzerland, a standard of $30 \mu\text{g}/\text{m}^3$ was adopted for nitrogen dioxide, which was even lower than the 2005 WHO recommendations [39, 40]. To date, seven countries have implemented the WHO recommendations for particulate matter into their national legislation (average of $10 \mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$) [38]

Calculating the burden of disease from air pollutants

- > Calculating the burden of disease reveals how strongly health risk factors affect the entire population and enables comparisons to show which risk factor gives rise to a particularly large number of diseases, reduced years of life expectancy or death. This can be used as a basis for setting priorities in prevention.
- > Typical risk factors used in these comparisons to calculate the burden of disease includes smoking status, malnutrition, air pollution, noise and lack of exercise.
- > The calculations follow a recognised method used on a regular basis by the WHO and other institutions. Comparative calculations are performed for individual countries and the entire world as part of the Global Burden of Disease Project conducted by the US-based "Institute for Health Metrics and Evaluation" (IHME). According to their results, air pollution is the ninth largest risk factor in Germany and is by far the greatest environmental risk factor for diseases and reduced life expectancy [49].
- > Each year, the European Environmental Agency calculates the burden of disease for certain air pollutants, namely particulate matter, nitrogen dioxide and ozone, in order to provide Europe and the individual Member States with information about the importance of the air pollutants and to study trends in the burden of disease over time [50].
- > These calculations are also performed in Germany to examine certain issues. Last year, for example, a study commissioned by the Environmental Office was published that investigated the burden of disease due to nitrogen dioxide in recent years [35]. It was determined that nitrogen dioxide, as an air pollutant or indicator of a mixture of air pollutants, has been observed to have adverse effects on life expectancy.

“Smoking is far more toxic and the dosage is much higher, which is why no damage can occur from comparatively low doses of air pollution”

- > There are many biological contexts in which the relationship between dosage and effect is not linear. Instead, the additional effects diminish as the dosage increases, as is well illustrated by the case of smoking: a smoker of 20 cigarettes a day has an around 100 % higher risk for a heart attack than a non-smoker [41]. Despite the far lower dosage, exposure to passive (second-hand) smoking on a regular basis or smoking one cigarette per day increases the risk of a heart attack by about 50 % as compared to individuals not exposed to cigarette smoke [42-45]. Long-term exposure to an additional 5 µg/m³ of particulate matter increases the probability of a heart attack by about 10 % [46]. Thus, the dose-to-effect ratio is not linear but rather flattens out as the dosage increases [41, 47]. If that non-linear relationship is taken into account properly, the effect sizes of exposure to the various air pollutants, passive smoking and active smoking fit together very well.
- > Smoking and air pollution also differ for other reasons:
 - The pattern of exposure is different: smoking involves intense exposure followed by breaks between cigarettes. Air pollution, on the other hand, causes continual daily and yearly exposure without interruption.
 - Active smoking primarily affects adults, whereas air pollution also affects fetuses, infants, asthmatic children and the elderly.
 - In principle, even though it can be incredibly difficult, we can control our smoking and quit on our own initiative whereas air pollution cannot, or only with great difficulty, be avoided.

“There is no typical pattern of toxicity”

- > **Particulate matter, ozone and nitrogen oxides** show a typical pattern of effects, such as oxidative stress and inflammatory reactions [e.g., 20, 48], with consequences similar to those of tobacco smoke. The best-known pollutant is particulate matter. We know from countless experiments and observational studies that particulate matter causes inflammatory reactions in the lungs and entire body, promotes blood clotting, causes cardiac arrhythmia, increases arteriosclerosis and alters lipid metabolism. In addition, particulate matter can penetrate the brain or affect a fetus. Those same biological changes can be seen in active and passive smokers. The same diseases are produced, including heart attacks, strokes, respiratory diseases and lung cancer.

“Nobody dies from particulate matter or nitrogen oxides”

- > That is true but according to that logic nobody dies from smoking, either. Nevertheless, we know that smoking, just like air pollution, is harmful over the long-term and can lead to potentially fatal diseases such as respiratory and cardiovascular illnesses. Such associations are only observable in long-term studies, however, rather than in the case of an individual patient or fatality. In the case of a single patient or a single death, it is almost always impossible to determine how the risk factors causally interacted to cause the illness or death. On the population scale, such associations can be expressed in terms of a reduction of life expectancy or years of life lost due to various risk factors such as smoking or air pollutants..

“The studies fail to take other risk factors into account and therefore result in a far too high burden of disease”

- > This statement is false. Other health risk factors are taken into account very precisely in high-quality epidemiological studies (e.g., smoking, physical inactivity, nutrition, education, income, etc.). The recognised methods of a high-quality observational study (epidemiological study) expressly require taking all further health risk factors into account.
- > It is likewise false to say that the studies merely compare the rural population with the urban population. On the contrary: most contemporary studies compare urban populations exposed to different degrees of pollution using estimates of long-term air pollution concentrations at each home address.

“The nitrogen dioxide limits in the USA are over twice as high, so nitrogen dioxide can’t be all that bad”

- > This is not quite true. The nitrogen dioxide limit in the USA (100 µg/m³) is truly higher than in the EU (40 µg/m³), but Americans have much stricter regulations on emissions, i.e., the level of nitrogen oxides in vehicle exhaust. This means they directly regulate the source (i.e., the automobile) much more stringently, so that German cars in America require a special upgrade. In the EU, 270 mg/km of nitrogen oxides in vehicle exhaust is currently allowed, whereas the maximum permissible emissions level in the USA is 100 mg/km (nitrogen oxides and organic methane gases), with the result that the overall average emissions level of a motor vehicle is less than 20 mg/km. On the other hand, the EU follows the WHO recommendations and has adopted the WHO’s recommended target value for atmospheric nitrogen dioxide. This means that the EU tends to focus on the concentrations of pollution that we actually breathe.
- > Moreover, when regulating air quality, different pollutants such as particulate matter and nitrogen dioxide must be analysed in combination. The US regulations impose a very strict limit on particulate matter (i.e., 12 µg/m³ for PM_{2.5}). In contrast, the EU limit on particulate matter is more than twice as high (25 µg/m³).

References

- WHO, Air quality guidelines. Global update 2005. 2006, Copenhagen: WHO Regional office for Europe.
- Federal Environmental Agency (UBA). Available from: <http://gis.uba.de/Website/luft/index.html>.
- WHO, Review of evidence on health aspects of air pollution – REVIHAAP. Technical Report. 2013, WHO Regional Office for Europe: Copenhagen. p. 309.
- IARC, Outdoor air pollution., in IARC Monographs on the evaluation of carcinogenic risks to humans. 2016, International Agency for Research on Cancer, Lyon.
- Thurston, G.D., et al., A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. *Eur Respir J*, 2017. 49(1).
- Stieb, D.M., et al., Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. *Environ Res*, 2012. 117: p. 100-11.
- Sun, X.L., et al., The associations between birth weight and exposure to fine particulate matter (PM_{2.5}) and its chemical constituents during pregnancy: A meta-analysis. *Environmental Pollution*, 2016. 211: p. 38-47.
- Schultz, E.S., A.A. Litonjua, and E. Melen, Effects of Long-Term Exposure to Traffic-Related Air Pollution on Lung Function in Children. *Current Allergy and Asthma Reports*, 2017. 17(6).
- Clifford, A., et al., Exposure to air pollution and cognitive functioning across the life course – A systematic literature review. *Environmental Research*, 2016. 147: p. 383-398.
- Eze, I.C., et al., Association between Ambient Air Pollution and Diabetes Mellitus in Europe and North America: Systematic Review and Meta-Analysis. *Environmental Health Perspectives*, 2015. 123(5): p. 381-389.
- He, D., et al., Association between particulate matter 2.5 and diabetes mellitus: A meta-analysis of cohort studies. *Journal of Diabetes Investigation*, 2017. 8(5): p. 687-696.
- Power, M.C., et al., Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: A systematic review of epidemiologic research. *Neurotoxicology*, 2016. 56: p. 235-253.
- Beelen, R., et al., Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet*, 2014. 383(9919): p. 785-95.
- Di, Q., et al., Air Pollution and Mortality in the Medicare Population. *New England Journal of Medicine*, 2017. 376(26): p. 2513-2522.
- Corrigan, A.E., et al., Fine particulate matters: The impact of air quality standards on cardiovascular mortality. *Environmental Research*, 2018. 161: p. 364-369.
- Federal Environmental Agency (UBA). particulate matter. Available from: <https://www.umweltbundesamt.de/themen/luft/luftschadstoffe/feinstaub>.
- Sutton, M.A., et al., European Nitrogen Assessment (ENA). 2011. 664.
- Federal Environmental Agency (UBA). ozone. Available from: <https://www.umweltbundesamt.de/themen/luft/luftschadstoffe/ozone>.
- Federal Environmental Agency (UBA). nitrogen oxides. Available from: <https://www.umweltbundesamt.de/themen/luft/luftschadstoffe/stickstoffoxide>.
- Kelly, F.J. and J.C. Fussell, Role of oxidative stress in cardiovascular disease outcomes following exposure to ambient air pollution. *Free Radical Biology and Medicine*, 2017. 110: p. 345-367.
- Cassee, F.R., et al., Particulate matter beyond mass: recent health evidence on the role of fractions, chemical constituents and sources of emission. *Inhalation Toxicology*, 2013. 25(14): p. 802-812.
- Halliwell, B., et al., Interaction of Nitrogen-Dioxide with Human Plasma – Antioxidant Depletion and Oxidative Damage. *Febs Letters*, 1992. 313(1): p. 62-66.
- EKL, Stickstoffhaltige Luftschadstoffe in der Schweiz [Nitrogen-bearing air pollutants in Switzerland]. Status-Report by the Swiss Federal Air Quality Committee. 2005: Bern. p. 168.
- Boldo, E., et al., Apheis: Health impact assessment of long-term exposure to PM_{2.5} in 23 European cities. *European Journal of Epidemiology*, 2006. 21(6): p. 449-458.
- Hoek, G., et al., Long-term air pollution exposure and cardio- respiratory mortality: a review. *Environ Health*, 2013. 12(1): p. 43.
- United States Environmental Protection Agency: US EPA, Integrated Science Assessment (ISA) for Particulate Matter (Final Report). 2009, US EPA: Washington, DC.
- United States Environmental Protection Agency: U.S. EPA, Integrated Science Assessment (ISA) of Ozone and Related Photochemical Oxidants (Final Report). 2013, U.S. EPA: Washington DC.
- Brown, J.S., Nitrogen dioxide exposure and airway responsiveness in individuals with asthma. *Inhalation Toxicology*, 2015. 27(1): p. 1-14.
- United States Environmental Protection Agency: US EPA, Integrated Science Assessment for Oxides of Nitrogen – Health Criteria. 2016, US EPA: Research Triangle Park, NC.
- Turner, M.C., et al., Long-Term Ozone Exposure and Mortality in a Large Prospective Study. *American Journal of Respiratory and Critical Care Medicine*, 2016. 193(10): p. 1134-1142.
- Beelen, R., et al., Long-term exposure to air pollution and cardiovascular mortality: an analysis of 22 European cohorts. *Epidemiology*, 2014. 25(3): p. 368-78.
- Brunekreef, B., et al., Effects of long-term exposure to traffic-related air pollution on respiratory and cardiovascular mortality in the Netherlands: The NLCS-AIR Study. 2009, Health Effects Institute: Boston, MA.
- Cesaroni, G., et al., Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect*, 2013. 121(3): p. 324-31.
- Carey, I.M., et al., Mortality associations with long-term exposure to outdoor air pollution in a national English cohort. *Am J Respir Crit Care Med*, 2013. 187(11): p. 1226-33.
- Schneider, A., et al., Quantifizierung von umweltbedingten Krankheitslast aufgrund der Stickstoffdioxid-Exposition in Germany [Quantification of environmentally caused burden of disease due to nitrogen dioxide exposure in Germany] in *Umwelt & Gesundheit*. 2018, Helmholtz Centre of Munich, Neuherberg: Dessau-Rosslau.
- Campen, M., et al., Engine exhaust particulate and gas phase contributions to vascular toxicity. *Inhal Toxicol*, 2014. 26(6): p. 353-60.
- WHO, Health risks of air pollution in Europe – HRAPIE project 2013: Copenhagen, Denmark.
- Kutlar Joss, M., et al., Time to harmonize national ambient air quality standards. *International Journal of Public Health*, 2017. 62(4): p. 453-462.
- EKL, particulate matter in der Switzerland 2013. 2013: Bern. p. 63.
- Swiss Federal Council, Swiss Clean Air Ordinance (LRV) of 16 December 1985 (version of 1 June 2018), in SR 814.318.142.1, Swiss Federal Council, Editor. 1985: Bern.
- Burnett, R.T., et al., An Integrated Risk Function for Estimating the Global Burden of Disease Attributable to Ambient Fine Particulate Matter Exposure. *Environmental Health Perspectives*, 2014. 122(4): p. 397-403.
- Office of the Surgeon General (US), The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. 2006, Centers for Disease Control and Prevention (US). Atlanta (GA).
- Oono, I.P., D.F. Mackay, and J.P. Pell, Meta-analysis of the association between secondhand smoke exposure and stroke. *Journal of Public Health*, 2011. 33(4): p. 496-502.
- Whincup, P.H., et al., Passive smoking and risk of coronary heart disease and stroke: prospective study with cotinine measurement. *BMJ*, 2004. 329(7459): p. 200-5.
- Barnoya, J. and S.A. Glantz, Cardiovascular effects of secondhand smoke – Nearly as large as smoking. *Circulation*, 2005. 111(20): p. 2684-2698.
- Vodonas, A., Y.A. Awad, and J. Schwartz, The concentration-response between long-term PM_{2.5} exposure and mortality: A meta-regression approach. *Environ Res*, 2018. 166: p. 677-689.
- Burnett, R., et al., Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci U S A*, 2018. 115(38): p. 9592-9597.
- Franklin, B.A., R. Brook, and C.A. Pope, Air Pollution and Cardiovascular Disease. *Current Problems in Cardiology*, 2015. 40(5): p. 207-238.
- The Institute for Health Metrics and Evaluation (IHME). What risk factors drive the most death and disability combined? 2017 [cited 2019 27.01.2019]; Available from: <http://www.health-data.org/germany>.
- European Environment Agency, Air Quality in Europe – 2017 report. 2017, European Environment Agency: Copenhagen. p. 78.