Ref. Ares(2016)1512245 - 30/03/2016
Ref. Ares(2018)2772570 - 29/05/2018

Horizon 2020

Societal Challenge: Improving the air quality and reducing the carbon footprint of European cities

Project: 690105 – ICARUS

Full project title:

Integrated Climate forcing and Air Pollution Reduction in Urban Systems

D4.3 Report on the methodology for estimating health effects of individuals or population groups and health impact results in the ICARUS participating cities

WP4: Population exposure and health impact assessment

Lead beneficiary: AUTH

Date: April 2018

Nature: Report

Dissemination level: Public

TABLE OF CONTENTS

Document Information

Grant Agreement Number	690105	**Acronym**	ICARUS
Full title	Integrated Climate forcing and Air pollution Reduction in Urban Systems		
Project URL			
Project Officer	Mirjam Witschke - Mirjam.WITSCHKE@ec.europa.eu		

Delivery date	**Contractual**	April 2018	**Actual**	May 2018
Status	Draft □		Final √	
Nature	Demonstrator □	Report √	Prototype □	Other □
Dissemination level	Confidential □	Public √		

Responsible Author (Partners)	**AUTH**			
Responsible Author	Denis Sarigiannis, Spyros Karakitsios		**Email**	denis@eng.auth.gr
	Partner	AUTH	**Phone**	+302310994562
Other partners (Institution)				

Document History

Name (Institution)	Date	Version
Aristotle University of Thessaloniki (AUTH)	February 2018	First Draft
Aristotle University of Thessaloniki (AUTH)	April 2018	Second draft
Aristotle University of Thessaloniki (AUTH)	May	Final

1 Introduction

Air pollution is still one of the major concerns regarding environmental factors of disease. According to World Health Organization (WHO), the joint effects of indoor and outdoor air pollution resulted in 556 000 premature deaths in the WHO European Region. What is also of particular importance is the disproportion of impacts among the low/middle income countries and the high-income countries.

Although air pollution is a well-recognized human health environmental threat, there are still many challenges that have to be addressed for estimating the related health impacts, that pertain for both exposure misclassification, as well as for the uncertainty of the concentration response functions itself. An additional problem is the limited mechanistic understanding on the way pollutants affect human health, especially considering that air pollution includes gaseous compounds (NO_2, O_3), particulates and various organic compounds such as VOCs, PAHs and dioxins. Thus, in order to address these issues, various methodological tools have to be employed, taking stock of the well-established knowledge on health impact assessment, as well as the opportunities provided by recent advances in risk assessment that account for internal dosimetry. This will allow the estimation of the actual impacts related to exposure to air pollution, thus, to drive effectively the cost–effectiveness and cost–benefit analyses of changes in air quality policies, which is one of the major aim of the ICARUS project. Given that, it is particularly important to assess all the impacts associated to the investigated policies and measures, thus to include the pollutants change that is associated with the relevant sector(s); If this is not the case, then the actual benefits might be underestimated and the overall capacity of the policies/measures might not be properly valuated.

Towards this aim, in ICARUS, we aim at a more precise translation of the environmental exposure into health effects, thus, various tools will be incorporated for enhancing the health impact assessment methodology. This will allow us to better translate the effect of different policies on emissions and public health. The concentration-response functions established by WHO in the HRAPIE project will be used for the health impact assessment of the major air pollutants (PM, CO, NO_2, O_3) as a starting point. Innovations beyond the state of the art will be incorporated taking into account (a) the integral of indoor/outdoor and in transit exposure and (b) when available, more refined methodologies that estimate intake and internal dose. These include the use of human respiratory tract deposition of particles accounting for their PAHs content and the use of a biokinetic model coupled to biology based does response relation for toxic organic pollutants such as benzene and dioxins.

2 Methodology

2.1 Health effects of common air pollutants

2.1.1 Particulate matter

2.1.1.1 Rationale

Particulate Matter is generally categorized on the basis of the size of the particles that reflects their aerodynamic diameter (e.g PM2.5 refers to particles with an aerodynamic diameter of less than 2.5μm). PM is made up of a wide range of components and are formed from a variety of sources and processes. Ambient air levels of PM comprise primary particles emitted directly into the atmosphere from combustion sources and secondary particles formed by chemical reactions in the air. Ambient air PM are released from both anthropogenic and natural sources (such as sea spray, Saharan dust or volcanos). The most common anthropogenic sources are stationary fuel combustion and transport. Road transport gives rise to primary particles from engine emissions, as well as various non-exhaust emissions such as tire and brake wear. Secondary PM is formed from emissions of ammonia, sulphur dioxide and oxides of nitrogen as well as from emissions of organic compounds from both combustion sources and vegetation. Both short-term and longterm exposure to ambient levels of PM are consistently associated with respiratory and cardiovascular illness and mortality as well as other adverse health effects. It is not currently possible to discern a threshold concentration below which there are no effects on public health. Fine particles are deposited in the lowest part of the human respiratory tract, where they can cause inflammation and a worsening of the condition of people with heart and lung diseases. In addition, they may carry surface-absorbed carcinogenic compounds into the lungs.

To estimate the health effects of PM exposure, well established epidemiological concentrations-response functions for outdoor PM from the meta-analysis of the HRAPIE report (WHO, 2013c) have been used. Differences in toxicity depending on particle composition (e.g. concentration and types of PAHs adsorbed) were not taken into account, since the current level of epidemiological knowledge does not allow the use of different concentration response functions based on the differences in composition, an opinion which is also supported by WHO (2007). Different concentration response-functions might be used only for particles of different aerodynamic diameter (PM10 and PM2.5). Other authors have come to similar conclusions. Based on the above, the CRFs for both short-term and long term health effects are given below.

2.1.1.2 Long-term health effects for PM

It is evident, that the changes in emissions are better described by PM2.5 than PM10 (Sarigiannis et al., 2015). As the relationship between PM measurements and health effects is log-linear, the conversion from PM10 CRFs to PM2.5 CRFs followed the mathematical formula below:

$$PM_{2.5}CRF = \exp\left(\ln\left(PM_{2.5}CRF\right)\right) = \exp\left(\frac{\ln\left(PM_{10}CRF\right)}{0.65}\right)$$

The detailed analysis for the extrapolation of PM10 concentration-response functions is given in the final deliverable of the HEIMTSA project case studies report (IOM, 2011), based on the initial concept described by WHO (2004).

The CRFs used for the selected health endpoints are given in detail in Table 1.

Table 1. Concentration response Functions (CRFs) for PM regarding long-term health effects

Health endpoint	CRF	Reference	Background rate	Age group
Mortality (all causes)	6.2% (95% CI: 4%, 8.3%) change per 10 µg/m^3 $PM_{2.5}$	(WHO, 2013c)	MDB (WHO, 2013b), rates for deaths from all natural causes (ICD-10 chapters I–XVIII, codes A–R) in each of the 53 countries of the WHO European Region, latest available data	Adults aged 30 years and older
Infant Mortality	4% (95% CI: 2%, 7%) change per 10 µg/m^3 PM_{10}	(Hurley et al., 2005; IOM, 2011)	145 post-neonatal deaths per 100,000 live births (9141 annual births) (EUROSTAT, 2011; WHO, 2008)	1 month to 1 year
Incidence of chronic bronchitis (adults)	11.7% (95% CI: 4%, 18.9%) change per 10 µg/m^3 PM_{10}	(WHO, 2013c)	390 new cases annually per 100,000 adults at risk (adjusted for remission - remission rate of 56.2%) (Schindler et al., 2009)	Adults aged 18 years and older
Chronic bronchitis (children)	8% (95% CI: -2%, 19%) change per 10 µg/m^3 PM_{10}	(Hoek et al., 2012; WHO, 2013c)	18.6% (Hoek et al., 2012)	Children aged 6–12 years
Cardiac hospital admissions	0.6% (95% CI: 0.3%, 0.9%) change per 10 µg/m^3 PM_{10}	(Hurley et al., 2005; IOM, 2011)	723 emergency cardiac admissions per 100,000 population, all ages, per year (Hurley et al., 2005):	All Ages

Respiratory hospital admissions	0.9% (95% CI: 0.7%, 1.0%) change per 10 µg/m^3 PM_{10}	(Hurley et al., 2005; IOM, 2011)	617 emergency respiratory hospital admissions per 100,000 population, all ages, per year (Hurley et al., 2005):	All Ages

2.1.1.3 Short-term health effects for PM

Table 2. Concentration response Functions (CRFs) for PM regarding short-term health effects

Health endpoint	CRF	Reference	Background rate	Age group
Mortality (all causes)	1.23% (95% CI: 0.45%, 2.01%) change per 10 µg/m^3 $PM_{2.5}$	(WHO, 2013c)	MDB (WHO, 2013b), rates for deaths from all natural causes (ICD-10 chapters I–XVIII, codes A–R) in each of the 53 countries of the WHO European Region, latest available data	All ages
Cardiac hospital admissions	0.91% (95% CI: 0.17%, 1.66%) change per 10 µg/m^3 $PM_{2.5}$	(WHO, 2013c)	European hospital morbidity database (WHO, 2013a), ICD-9 codes CVD: 390–429; respiratory: 460–519 (ICD-10 codes I00–I52; J00–J99)	All Ages
Respiratory hospital admissions	1.9% (95% CI: 0.99%, 4.02%) change per 10 µg/m^3 $PM_{2.5}$	(WHO, 2013c)	European hospital morbidity database (WHO, 2013a), ICD-9 codes CVD: 390–429; respiratory: 460–519 (ICD-10 codes I00–I52; J00–J99)	All Ages
Restricted activity days (RADs)	4.7 % (95% CI: 4.2%, 5.3%) change per 10 µg/m^3 $PM_{2.5}$	(WHO, 2013c)	19 RADs per person per year: baseline rate from the Ostro and Rothschild (1989) study	All Ages

Work days lost	4.6% (95% CI: 3.9%, 5.3%) change per 10 µg/m^3 $PM_{2.5}$	(WHO, 2013c)	European Health for All database (2013, WHO)	Working- age population (age 20–65 years)
Incidence of asthma symptoms in asthmatic children	2.8% (95% CI: 0.6%, 5.1%) change per 10 µg/m^3 PM_{10}	(WHO, 2013c)	(Lai et al., 2009) – western Europe: 4.9%; northern and eastern Europe: 3.5%. Daily incidence of symptoms in this group: 17% (interpolation from several panel studies)	Children aged 5–19 years

2.1.2 Black carbon

Black Carbon (BC) is a term aiming at describing carbon as measured by light absorption methods. BC originates from multiple sources related to combustion engines, mostly related to diesel, as well as other less elaborate combustion processes such as biomass and coal burning, which in turn is associated with many sectors of urban activities relevant to the ICARUS project. As a result, BC is in practice a more generic indicator of the multitude composition of combustion sources of particulate matter. At the moment there is limited toxicological *in vivo* and *in vitro* information on BC, however it is hypothesized that BC does not exert direct properties, but is acting as a substrate for strong adsorption of toxic components such as PAHs, quinones, nickel, vanadium and arsenic, related to emissions from various sectors involving combustion. As such, BC levels are associated with both PM mass concentrations, as well as their toxic burden. The latter is highlighted on the proposed CRF for BC associated to all-causes mortality, where an increase of 10 µg/m^3 of BC, has been associated with an increase of 60% of all-causes mortality.

Table 3. Black Carbon (BC) related all-cause mortality

Health endpoint	CRF	Reference	Background rate	Age group
Mortality, All causes	60% (95% CI: 10%, 110%) change per 10 µg/m^3 Black Carbon	(Janssen et al., 2011)	MDB (WHO, 2013b), rates for deaths from all natural causes (ICD-10 chapters I–XVIII, codes A–R) in each of the 53 countries of the WHO European Region, latest available data	30+ years

2.1.3 Ozone

O_3 is the tri-atomic form of molecular oxygen. It is a strong oxidising agent, which is considerd highly reactive. In Europe, Background levels of O_3 are usually below 15 ppb; however, under high solar radiation conditions (usually in summer) concentrations up to 100 ppb are observed, associated with photochemical smog episodes. According to the Ambient Air Quality Directive (EU, 2008), a maximum daily 8-hour mean threshold of 120 μg/m^3 has been established. Based on the health effects of ozone, several CRFs have been widely accepted for both long-term and (mainly) short-term health effects.

2.1.3.1 Long-term health effects of ozone

Health endpoint	CRF	Reference	Background rate	Age group
Mortality, respiratory diseases	1.4% (95% CI: 0.5%, 2.4%) change per 10 μg/m^3 O_3	(WHO, 2013c)	MDB (WHO, 2013b), ICD- 10 codes J00–J99	30+ years

2.1.3.2 Short-term health effects of ozone

Health endpoint	CRF	Reference	Background rate	Age group
Mortality, all (natural) causes, (>35 ppb (>70 μg/m³))	0.29% (95% CI: 0.14%, 0.43%) change per 10 μg/m^3 O_3	(WHO, 2013c)	MDB (WHO, 2013b), ICD-10 chapters I–XVIII, codes A–R	All ages
Mortality, all (natural) causes, (>10 ppb (>20 μg/m³))	0.29% (95% CI: 0.14%, 0.43%) change per 10 μg/m^3 O_3	(WHO, 2013c)	MDB (WHO, 2013b), ICD-10 chapters I–XVIII, codes A–R	All Ages
Mortality, CVDs and respiratory diseases (>35 ppb (>70 μg/m³))	CDV: 0.49% (95% CI: 0.13%, 0.85%) change per 10 μg/m^3 O_3 Respiratory: 0.29% (95% CI: 0.099%, 0.7%) change per 10 μg/m^3 O_3	(WHO, 2013c)	MDB (WHO, 2013b), ICD-10 codes CVD: I00–I99; respiratory: J00–J99	All Ages
Mortality, CVDs and respiratory diseases (>10 ppb (>20 μg/m³))	CDV: 0.49% (95% CI: 0.13%, 0.85%) change per 10 μg/m^3 O_3	(WHO, 2013c)	MDB (WHO, 2013b), ICD-10 codes CVD: I00–I99; respiratory: J00–J99	All Ages

	Respiratory: 0.29% (95% CI: 0.099%, 0.7%) change per 10 µg/m^3 O_3			
Hospital admissions, CVDs (excluding stroke) and respiratory disease(>35 ppb (>70 µg/m³))	CDV: 0.89% (95% CI: 0.5%, 1.27%) change per 10 µg/m^3 O_3 Respiratory: 0.44% (95% CI: 0.07%, 0.83%) change per 10 µg/m^3 O_3	(WHO, 2013c)	European hospital morbidity database (WHO, 2013a), ICD-9 codes CVD: 390–429; respiratory: 460–519 (ICD-10 codes I00–I52; J00–J99)	Age 65+ years
Hospital admissions, CVDs (excluding stroke) and respiratory disease(>10 ppb (>20 µg/m³))	CDV: 0.89% (95% CI: 0.5%, 1.27%) change per 10 µg/m^3 O_3 Respiratory: 0.44% (95% CI: 0.07%, 0.83%) change per 10 µg/m^3 O_3	(WHO, 2013c)	European hospital morbidity database (WHO, 2013a), ICD-9 codes CVD: 390–429; respiratory: 460–519 (ICD-10 codes I00–I52; J00–J99)	Age 65+ years
Minor restricted activity days (MRADs) (>35 ppb (>70 µg/m³))	1.54% (95% CI: 0.60%, 2.49%) change per 10 µg/m^3 O_3	(WHO, 2013c)	7.8 days per year, based on Ostro and Rothschild (1989)	All Ages
MRADs (>10 ppb (>20 µg/m³))	1.54% (95% CI: 0.60%, 2.49%) change per 10 µg/m^3 O_3	(WHO, 2013c)	7.8 days per year, based on Ostro and Rothschild (1989)	All Ages

2.1.4 NO_2

The main health effects associated to exposure to NO_2 are shortness of breath or coughing and enhanced risk of respiratory disease. NO_2 is associated with several respiratory adverse effects on human health. At high levels NO_2 causes inflammation of the airways. Long-term exposure may affect lung function and respiratory symptoms. NO_2 also enhances the response to allergens in sensitive individuals. Nitrogen dioxide can irritate the lungs and lower resistance to respiratory infections such as influenza. Continued or frequent exposure to concentrations that are typically much higher than those normally found in the ambient air may cause increased incidence of acute respiratory illness in children. The CRFs for long term and short health effects of NO_2 are given below.

2.1.4.1 Long-term health effects of NO_2

Health endpoint	CRF	Reference	Background rate	Age group
Mortality, all (natural causes>20 µg/m³)	5.50% (95% CI: 3.10%, 8.0%) change per 10 µg/m^3 NO_2	(WHO, 2013c)	MDB (WHO, 2013b), rates for deaths from all natural causes (ICD-10 chapters I–XVIII, codes A–R) in each of the 53 WHO Regional Office for Europe countries, latest available data	Age 30+ years
Prevalence of bronchitic symptoms in asthmatic	2.1% (95% CI: 0.099%, 6.00%) per 1 µg/m³ change in annual mean NO2	(WHO, 2013c)	Background rate of asthmatic children, "asthma ever", in Lai et al. (2009) – western Europe: 15.8%, standard deviation (SD) 7.8%; northern and eastern Europe: 5.1%, SD 2.7%, with a recommended alternative of "severe wheeze" in Lai et al. (2009) – western Europe: 4.9%; northern and eastern Europe: 3.5% Prevalence of bronchitic symptoms among asthmatic children 21.1% to 38.7% (McConnell et al., 2003; Migliore et al., 2009)	Children aged 5–14 years

2.1.4.2 Short-term health effects of NO_2

Health endpoint	CRF	Reference	Background rate	Age group

Mortality (all natural causes) (daily maximum 1-hour mean)	0.27% (95% CI: 0.16%, 0.38%) change per 10 µg/m^3 NO_2	(WHO, 2013c)	MDB (WHO, 2013b), rates for deaths from all natural causes (ICD-10 chapters I–XVIII, codes A–R) in each of the 53 countries of the WHO European Region, latest available data	All ages
Hospital admissions, respiratory diseases (daily maximum 1-hour mean)	0.15% (95% CI: 0.099%, 0.38%) change per 10 µg/m^3 NO_2	(WHO, 2013c)	European hospital morbidity database (2013, WHO)	All Ages
Hospital admissions, respiratory diseases (24-hour mean)	1.8% (95% CI: 1.15%, 2.45%) change per 10 µg/m^3 NO_2	(WHO, 2013c)	European hospital morbidity database (2013, WHO)	All Ages

2.1.5 Carbon monoxide

Carbon Monoxide (CO) is a colourless, odourless, tasteless gas that is slightly lighter than air. Natural background levels of CO fall in the range of 10-200 ppb. Levels in urban areas are highly variable, depending upon weather conditions and traffic density. 8-hour mean values are generally less than 10 ppm (12 mgm^{-3}) but have been known to be as high as 500 ppm (600 mgm^{-3}). The European limit value for the maximum daily 8-hour mean concentrations of CO is set to 10 mg/m^3 (EU, 2000). Based on the available measurements, it can be concluded that in EU the CO ambient concentrations above the limit value is very localised and infrequent, and is limited to a very few areas near traffic and industry. The main health effects related to exposure to CO are: headaches, dizziness, slows mental processes, and at high levels can lead to death. CO prevents the normal transport of oxygen by the blood. This can lead to a significant reduction in the supply of oxygen to the heart, particularly in people suffering from heart disease. Although several studies have identified associations between elevated short-term ambient air carbon monoxide and increasing mortality risk when carbon monoxide is considered in single-pollutant models, these associations were getting weak when models were adjusted for co-exposure to other pollutants (ATSDR, 2012). Thus, for Europe, the most comprehensive analysis is the one considered by Samoli et al. (2007), where significant associations of CO were identified with total and cardiovascular mortality.

2.1.5.1 Short-term health effects of CO

Health endpoint	CRF	Reference	Background rate	Age group

Mortality (all natural causes) (2-day mean)	1.2% (95% CI: 0.63%, 1.77%) change per 1 mg/m^3 CO	(Samoli et al., 2007)	MDB (WHO, 2013b), rates for deaths from all natural causes (ICD-10 chapters I–XVIII, codes A–R) in each of the 53 countries of the WHO European Region, latest available data	All ages
Mortality (CVDs) (2-day mean)	1.25% (95% CI: 0.3%, 2.21%) change per 1 mg/m^3 CO	(Samoli et al., 2007)	MDB (WHO, 2013b), ICD-10 codes CVD: I00–I99	All ages

2.1.6 Relative risk, attributable burden and health impact calculation

In order to translate the CRFs into impact, the following steps have to be follow:

Firstly, relative risk is calculated for the average concentration X, using the following formula:

$$RR = CRF^{\left(\frac{X}{10}\right)}$$

The exponential is used because the original analyses used a proportional hazard, i.e. log-linear, regression model. From this relative risk is derived the attributable fraction ***AF*** is derived as follows:

$$AF = \left(\frac{RR-1}{RR}\right)$$

and this is multiplied by the background rate of disease ***BR*** to derive the estimated health impact ***HI*** as the number of cases expected to present the respective adverse health outcome in the population of interest ***P***. Thus, the health impact ***HI*** is given as:

$$HI = AF \cdot BR \cdot F$$

The actual burden of mortality, (i.e. the attributable death due to $PM_{2.5}$ exposure) is expressed in years of life lost (***YLL***). To estimate *YLL*, life tables (WHO, 2014) are employed, where national population and the corresponding mortality data per age band should be used. These data are used to derive the population-weighed annual average concentration for a pollutant *C*. The attributable fraction *AF* is multiplied with the background mortality rate *D* for the given age band in order to compute the number of attributable deaths (***AD***) per age band.

$$AD = AF \cdot D$$

The number of attributable deaths *AD* per age band is then multiplied with the expected years of life (Y_{LE}) for the given age band.

$$YLL = AD \cdot Y_{LE}$$

Demographic data regarding the population and mortality/morbidity rates distribution for the several age groups are usually obtained from the EUROSTAT databases (EUROSTAT, 2011). Additional data for background rate of disease and mortality can be obtained by WHO (2008) or from local and national authorities.

2.2 Other air pollutants

2.2.1 Benzene (in the view of BTEX mixture)

2.2.1.1 Rationale

Benzene is an air toxic emitted from gasoline service stations (Karakitsios et al., 2007), gasoline (mainly) motor vehicle exhaust and fuel evaporation, the burning of coal and oil, and to a lesser extend to various other combustion sources. Human exposure to benzene has been associated with a range of acute and long-term adverse health effects and diseases, including cancer and aplastic anemia (Rinsky et al., 1987b). Benzene is a recognized human carcinogen that interacts with the genetic material and, as such, no absolutely safe level can be specified in ambient air. Studies in workers exposed to high levels have shown an excessive risk of leukemia (Wong, 1987). Exposure can occur occupationally and domestically as a result of the ubiquitous use of benzene-containing petroleum products, including motor fuels and solvents (Perbellini et al., 1988). Active and passive exposure to tobacco smoke is also a significant source of exposure (Karakitsios et al., 2010; Lai et al., 2007). Since benzene is highly volatile, exposure occurs mostly through inhalation.

2.2.1.2 Benzene PBPK model

The whole metabolic chain of benzene (Figure 1) was modeled starting from previously developed PBPK/PD models for benzene metabolism in mice (Manning et al., 2010) and its extrapolation to humans (Yokley et al., 2006). The model evaluates tissue levels of benzene, benzene oxide (BO), phenol (PH), and hydroquinone (HQ), as well as the total amounts of muconic acid (MA), phenylmercapturic acid (PMA), phenol conjugates, hydroquinone conjugates, and total catechol produced. For benzene oxide, phenol, and hydroquinone, the body is divided into five compartments: kidney; liver; fat; rapidly perfused tissues (RTP), and slowly perfused tissues (PPT). As for the benzene model the liver is subdivided into three compartments of equal volume according to the specific enzymatic distribution. The further metabolism of BO, PH and HQ is supposed to occur in the liver (main metabolism organ) and to a lesser extent in the kidney.

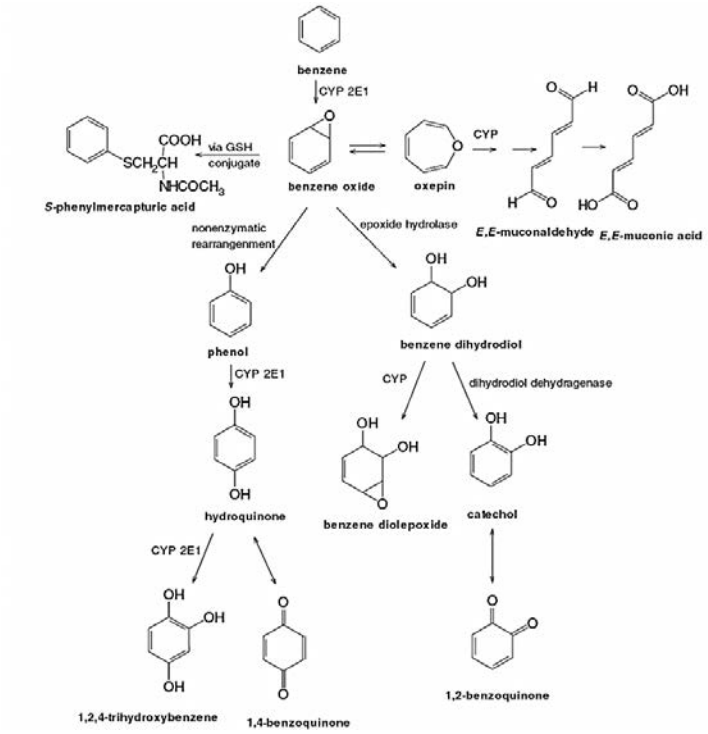

Figure 1. Metabolic chain of benzene to its primary metabolites

The PBPK/PD model results were validated through successive and complementary steps: first we validated the interaction mechanism among toluene, xylene and ethylbenzene; then the biokinetics of benzene and finally the metabolic chain of benzene. Each one of these validations was carried out by comparing the model results with independent experimental data reported in literature (Pekari et al., 1992; Tardif et al., 1997; Waidyanatha et al., 2004). Results show that the PBPK/PD model developed in the present study provides accurate estimations of the kinetics of the BTEX mixture in the human body. This also confirms that the mechanism of interaction based on the competitive inhibition between the four VOCs in the mixture describes the experimental data adequately. Some minor discrepancies from the empirical data are likely to be attributed to the use of reference physiological parameters in the absence of actual parameters and inherent variability in the experimental data.

The high potential toxicity of benzene metabolites associated with leukaemia risk in humans, suggested taking into account in more detail the metabolic chain from benzene to its key metabolites through a more refined PBPK model for that chemical. The whole metabolic chain of benzene was modelled starting from previously developed PBPK models for benzene metabolism in mice and its extrapolation to humans. The model (Figure 2) evaluates tissue levels of benzene, benzene oxide (BO), phenol (PH), and hydroquinone (HQ), as well as the total amounts of muconic acid (MA), phenylmercapturic acid (PMA), phenol conjugates, hydroquinone conjugates, and total catechol produced. For benzene oxide, phenol, and hydroquinone, the body is divided into five compartments: kidney; liver; fat; rapidly perfused tissues (RTP), and slowly perfused tissues (PPT). As for the benzene model the liver is subdivided into three compartments of equal volume according to the specific enzymatic distribution. The further metabolism of BO, PH and HQ is supposed to occur in the liver (main metabolism organ) and to a lesser extent in the kidney.

The following metabolic transformations (mediated by CYP2E1) are supposed to occur in zone 3 of the liver as well as in the kidney:

benzene → benzene oxide

phenol → hydroquinone

phenol → catechol

hydroquinone → trihydroxy benzene

The equations describing these metabolic reactions are given hereafter.

CYP2E1 activity in the liver (zone 3 of the liver):

$$RM_{BO,Liver3}^{BZ} = k_1 \frac{V_{2E1} C_{Liver3}^{BZ}}{D_L} C^{MP} \frac{T_L}{3}$$

Benzene to Benzene Oxide

$$RM_{HQ,Liver3}^{PH} = k_5 \frac{V_{2E1} C_{Liver3}^{PH}}{D_L} C^{MP} \frac{T_L}{3}$$

Phenol to Hydroquinone

$$RM_{CAT,Liver3}^{PH} = k_6 \frac{V_{2E1} C_{Liver3}^{PH}}{D_L} C^{MP} \frac{T_L}{3}$$

Phenol to Catechol

$$RM_{THB,Liver3}^{HQ} = k_7 \frac{V_{2E1} C_{Liver3}^{HQ}}{D_L} C^{MP} \frac{T_L}{3}$$

Hydroquinone to Trihydroxy benzene

where:

$$D_L = 1 + A^{BZ} C_{Liver3}^{BZ} + A^{PH} C_{Liver3}^{PH} + A^{HQ} C_{Liver3}^{HQ}$$

Since the kidney contains approximately 10% of the concentration of CYP2E1 found in the liver, it is assumed that relative to the metabolism in the liver, 10% of the metabolism mediated by CYP2E1 is in the kidney. The V2E1, that is the CYP2E1 specific activity as determined by the oxidation of p-nitrophenol to p-nitrocatechol, is scaled by 10% to give us the rate equations for the metabolisms using CYP2E1 in the kidney:

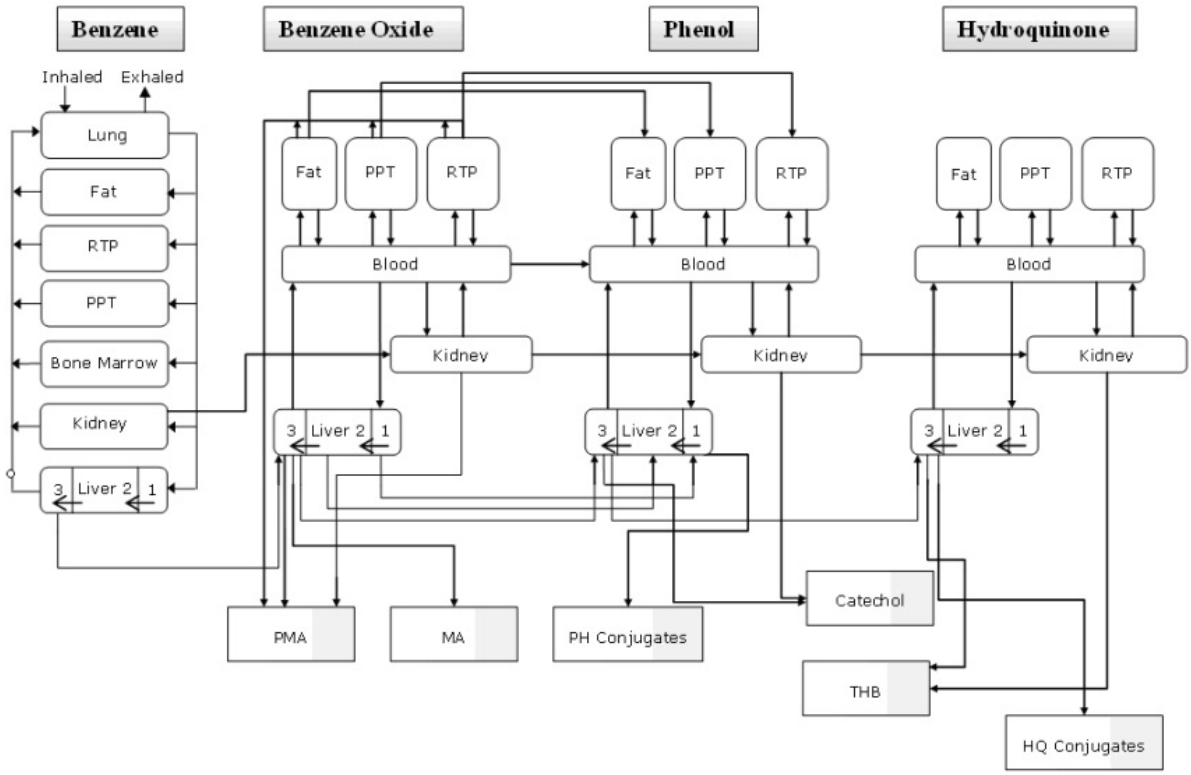

Figure 2. Conceptual representation of benzene PBPK model

CYP2E1 activity in the kidney:

$$RM_{BO,Kidney}^{BZ} = k_1 \frac{V_{2E1} C_K^{BZ}}{10 D_K} C^{MP} T_K$$

Benzene to Benzene Oxide

$$RM_{HQ,Kidney}^{PH} = k_5 \frac{V_{2E1} C_K^{PH}}{10 D_K} C^{MP} T_K$$

Phenol to Hydroquinone

$$RM_{CAT,Kidney}^{PH} = k_6 \frac{V_{2E1} C_K^{PH}}{10 D_K} C^{MP} T_K$$

Phenol to Catechol

$$RM_{THB,Kidney}^{HQ} = k_7 \frac{V_{2E1} C_K^{HQ}}{D_K} C^{MP} T_K$$

Hydroquinone to Trihydroxy benzene

where:

$$D_K = 1 + A^{BZ} C_{Kidney}^{BZ} + A^{PH} C_{Kidney}^{PH} + A^{HQ} C_{Kidney}^{HQ}$$

and T_L and T_K are respectively the total mass of the liver and the total mass of the kidney. Assuming that tissue has the same density as water, we obtain:

$$T_j = V_j \times \frac{10^3 g}{1L}$$

where ***j*** could be the liver (L) or the kidney (K)

Since epoxide hydrolase, which mediates the metabolism of benzene oxide to muconic acid, is found in the centrilobular region (zone 3) of the liver, this metabolism is also assumed to occur in the zone 3 of the liver and it can be described by the first-order equation:

$$RM_{MA,Liver3}^{BO} = k_4 C_{Liver3}^{BO} \frac{V_L}{3}$$

Benzene Oxide to Muconic Acid

The metabolism of hydroquinone to its conjugates is assumed to occur in zone 3 since the glucuronidation capacity is greater in this region. It can be represented by the equation for glucuronidation from:

$$RM_{Conj,Liver3}^{HQ} = \frac{V_{HQ} C_{Liver3}^{HQ}}{K_m^{HQ} + C_{Liver3}^{HQ}} C^{MP} \frac{T_L}{3}$$

Hydroquinone to its conjugates

Since the sulfation takes place primarily in zone 1 of the liver, the conjugation of phenol was simulated as occurring only in zone 1 and is represented by the following equation:

$$RM_{Conj,Liver1}^{PH} = \left(\frac{V_{PH1} C_{Liver1}^{PH}}{K_{m,1}^{PH} + C_{Liver1}^{PH}} + \frac{V_{PH2} C_{Liver1}^{PH}}{K_{m,2}^{PH} + C_{Liver1}^{PH}} \right) C^{CP} \frac{T_L}{3}$$

Phenol to its conjugates

The metabolism of benzene oxide to phenol is nonenzymatic, so we assumed that this metabolism occurs in all compartments. This process is described by the first-order equation:

$$RM_{PH,j}^{BO} = k_2 C_j^{BO} V_j$$

Benzene Oxide to Phenol

where ***j*** is the compartment index.

Finally, glutathione S-transferase, which is required for the metabolism of benzene oxide to phenylmercapturic acid, is found in tissue such as the liver, kidney, muscle, and heart. Within the liver, glutathione S-transferase is found primarily in the plate-limiting hepatocytes of the central vein. Thus, we consider first-order metabolism to occur in the slowly and rapidly perfused tissues, the fat, the kidney, the blood, and the third zone of the liver according to the following equation:

$$RM_{PMA,j}^{BO} = k_3 C_j^{BO} V_j$$

2.2.1.3 Benzene cancer risk

The final building block for estimating the leukemia associated risk, is the definition of the respective mathematical model of human pathology. Pathology modeling has focused on a few ill-health conditions such as cancer and organ malfunction (e.g. heart disease) to date. This approach varies from a purely phenomenological one, including statistical descriptions of the link between toxic insult and health effect, to sets of differential equations describing mechanisms of action and partial differential equation models that take into account the presence of xenobiotics in specific parts of organs, up to more advanced mathematical techniques including cellular automata, neural networks and other artificial intelligence methods for quantifying the link.

According to Schollnberger et al (2006), the earliest approaches to mathematically investigate cancer began in the early 1950s. Nordling (1953) and Stocks (1953) proposed that several successive mutations in a cell would be necessary to explain the fact that, for many carcinomas, the incidence rate varies as a power function of age. This has been quantitatively formulated by Armitage and Doll (1954) in one of the best-known cancer models, a multi-stage model that accounts for the relationship between age and cancer incidence. The model reflects the number of stages needed for a normal cell to develop into a malignant cell. For the Armitage–Doll multi-stage model, no clonal growth was assumed. Because of discrepancies with the observed number of biological stages, Armitage and Doll further developed their model into one of two stages, with exponentially growing clones (Armitage and Doll, 1957). The Armitage–Doll two-stage model has limitations in cancer risk assessment because it assumed deterministic cell growth. When the growth rate is small, it is more appropriate to use a stochastic model because the probability of extinction of clones, which is not considered in a deterministic model, cannot be neglected. This led to the development of stochastic cancer models (Knudson Jr, 1971; Moolgavkar, 1978; Moolgavkar and Knudson Jr, 1981; Moolgavkar and Venzon, 1979; Tan, 1991). Stochastic cell growth of intermediate cells is assumed for the stochastic two-mutation model with clonal expansion. This two-step clonal expansion (TSCE) model is the best-known multi-step model and was developed by Moolgavkar, Venzon and Knudson (Moolgavkar, 1978; Moolgavkar and Knudson Jr, 1981; Moolgavkar and Venzon, 1979), after whom it is known as the MVK model. In contrast with the Armitage–Doll model, there is a considerable amount of experimental data supporting the stochastic two-mutation model (Chen, 1993).

Among the four VOCs considered in this work (benzene, toluene, ethylbenzene and xylene), benzene represents certainly the most potentially dangerous to human health. Chronic exposure to low levels of benzene may produce reversible decreases in blood cell numbers but, at higher levels, an irreversible bone marrow depression, with pancytopenia, may establish. This pathological condition is called aplastic anemia. Pancytopenia can occur also in the so-called myelodisplastic syndrome (MDS). Benzene MDS usually proceeds to leukemia, mostly acute myeloid leukemia (AML). The approaches taken to assess the cancer risk from benzene exposure have been varied and have resulted in risk estimates that range considerably in magnitude. The U.S. EPA (2000) used the Goodyear Pliofilm study (Rinsky et al., 1987a; Rinsky et al., 1981) for their quantitative risk estimation. They estimated a range of $2.2 \cdot 10^{-6}$ to $7.8 \cdot 10^{-6}$ as the increase in the lifetime risk of an individual who is exposed for a lifetime to 1 ug/m^3 benzene in air. This is based on a linear model and extrapolates to air concentrations of 1.3 to 4.5 ug/m^3 for a risk level of 1 in 100,000. The approach used by Crump directly linked external

exposure to cancer risk using the Area Under the Curve (AUC) as the dose metric. Finally, an empirical statistical D-R model based on Maximum Likelihood Estimation (MLE) is derived, based on experimental data about cancer incidence as function of the exposure. The dose-response model developed by Crump (1994) takes the following form:

$$P(x) = 1 - e^{\left[-\left(0.00145x + 0.00013x^2\right)\right]}$$

where ***P(x)*** represents the cancer probability attributable to ***x*** mg/kg/day of administered benzene to male mice. This equation implies that, at very low administered doses, the risk varies linearly with dose. To extend it to humans the authors of this study assumed that the same administered quantities of benzene "produce equal cancer risk in humans and animals, independent of the route of exposure". A key weakness of this approach is that AUC might not be the best choice of dose metric for benzene since it does not distinguish between dose histories having different time evolution if they have the same integrated total dose. For these situations the risk estimate based on the AUC will produce the same risk, although many experiments have shown that different time patterns of benzene dose administration with the same AUC produce very different profiles of benzene metabolites (Crump and Allen, 1984) and very different hematotoxic effects.

In this work we applied a method, originally developed by Cox Jr. (1996), based on the decomposition of the dose-response relationship into a set of causal micro-relations, each one describing a separate biologic process. Instead of evaluating the relationship between administered dose and cancer risk 'directly' through an empirical-statistical model, this relationship is thus decomposed into two different parts: the first one links the administered dose to the total amount of metabolites produced (internal dose), while the second connects the internal dose to the probability of cancer.

The first relation is provided by the results of the PBPK/PD model, which has already been validated against human biomonitoring data (Sarigiannis and Gotti, 2008). The statistical relation between internal dose and cancer probability was calculated using a parameterized function (1) from Crump and Allen (1984). In particular, the administered dose was calculated assuming an average person of 70 kg (adult) who inhales 10 m^3 of air in 8 hours for an occupation period of 40 years over a life of 70 years.

The next step was to derive an empirical statistical relation linking the internal dose to cancer probability. This was found to be the following:

$$P(y) = 1 - e^{\left[-0.04296940\,y + 0.02633730\,y^2 - 0.00764081\,y^3\right]}$$

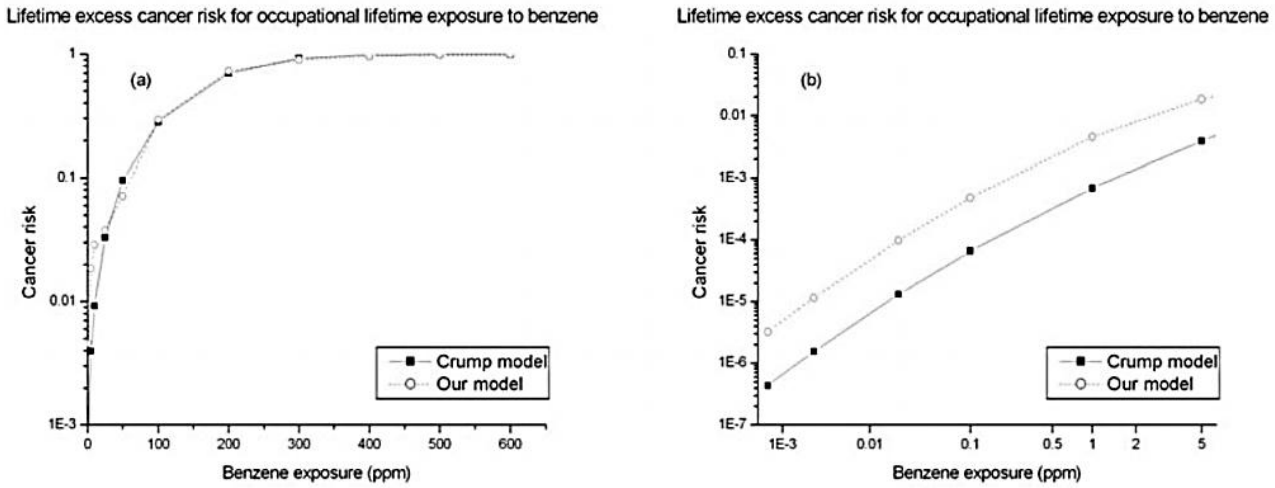

***Figure 3**. (a) lifetime excess cancer risk for 8hr/day lifetime inhalation exposure to benzene as predicted by Crump and Allen and our model. (b) the same at low doses*

The standard error for the model parameters varied from 23% (for the linear term) to 9% (for the cubic term). This relationship incorporates the results of the PBPK/PD models that allow us to estimate the actual biologically effective dose (BED) of benzene metabolites in the bone marrow (the main target tissue for leukemia). BED of benzene metabolites is associated with the intake dose of both benzene and other VOCs present in the BTEX mixture. It has to be noted, however, that metabolic inhibition of benzene by co-exposure to toluene, ethylbenzene and xylenes is dose-dependent. This kind of biochemical interaction is usually low at very low levels of exposure. Thus, cancer probability, ***P(y)***, can be linked mathematically to the average benzene exposure level, ***y***, even though the cancer potency of benzene is attributed to its metabolites. In ***Figure 3*** the estimated cancer risk as a function of the external benzene concentration as predicted by Crump and Allen model (solid line) and by our model (dashed line) is given.

2.2.2 Benzo[a]pyrene and PAHs

2.2.2.1 Rationale

Several epidemiological studies have shown the adverse health effects of airborne particulate matter deposited in the human respiratory tract (HRT) (Kennedy, 2007; Pope Iii and Dockery, 2006). HRT deposition of a particular particle depends on its aerodynamic diameter (d_p). Particulate matter can be divided to coarse particles (d_p>2.5 μm), which are mainly deposited in the upper respiratory system, fine particles (0.1<d_p<2.5 μm), which are deposited in the tracheobronchial region of the human respiratory tract, and ultrafine particles (d_p<0.1 μm) which are deposited in the pulmonary/alveolar region (Lin et al., 2008). As a result, xenobiotics contained in ultrafine particles can be easily translocated in the human body via systemic circulation.

Genotoxic effects of inhaled particulate matter are mainly attributed to adsorbed polycyclic aromatic hydrocarbons (PAHs). PAHs include a variety of semi-volatile organic compounds of low vapor pressure that can be transferred in long distances as they are mostly adsorbed in fine and ultrafine particles

(Dvorská et al., 2012; Venkataraman et al., 1994). Such compounds may be retained for long in human tissue due to their high lipophilicity. About 90% of PAHs are emitted by vehicles (Nielsen, 1996). Other sources include industry, biomass combustion, coke and tar production, as well as tobacco smoke (Freeman and Cattell, 1990; Masclet et al., 1987). Including benzo[a]pyrene (B[a]P), the only PAH classified as known carcinogen to humans by IARC, the most hazardous PAHs are mainly distributed in the particulate phase (IARC, 2010). After human exposure to particulate-bound PAHs, the compounds are distributed in alveolar (80%) and tracheobronchial region (20%) of the HRT. However, the ultimate dose of more toxic substances and their carcinogenic metabolites is much greater in the latter region due to the lower rate of diffusion through the bronchial epithelium. Ultimate PAH metabolites may alter the replication and transcription mechanisms of DNA and induce tumors (Armstrong et al., 1994; Boström et al., 2002). Taking as basis the toxicity of benzo[a]pyrene and using Toxic Equivalent Factors (TEFs), it is possible to calculate the overall toxicity (Toxic Equivalent Concentration, TEQ) of the PAHs mixture assuming that the TEF of benzo[a]pyrene is equal to 1 (Nisbet and LaGoy, 1992). The majority of studies related to carcinogenic potential of PAHs (e.g. (Wiriya et al., 2013; Yu et al., 2008) apply the EPA equation or calculate the Incremental Life Cancer Risk (ILCR) without any differentiation between age groups of the individuals exposed. HRT deposition modeling has been applied only by Chiang and Liao (2006) to determine the PM mass lung/indoor ratio after exposure to heavy incense burning in a Taiwanese temple and the PM size distribution in different HRT regions (these results are not linked with PM-bound PAHs), and by (Zhang et al., 2012) to estimate the distribution of PAHs to particles of different diameter and calculating Lifetime Cancer Risk (LCR).

2.2.2.2 Human respiratory tract (HRT) deposition

HRT particle deposition modeling is applied for the determination of PM deposition fraction (DF) to the three parts of the pulmonary system in order to estimate the internal dose of PAHs. Major mechanisms of PM deposition across HRT include diffusion, sedimentation and impaction. Secondary mechanisms involve interception and electrostatic deposition. Different HRT regions involve different deposition mechanisms, with regard to different PM size as follows:

- Naso-pharyngeal region (or upper respiratory tract – URT): impaction, sedimentation, electrostatic (particles > 1 μm)
- Tracheo-bronchial (TB) region: impaction, sedimentation, diffusion (particles < 1 μm)
- Pulmonary (P) region: sedimentation, diffusion (particles < 0.1 μm)

Several parameters affect HRT deposition, including PM properties (concentration and size distribution), air flow parameters (lung capacity and breathing frequency) and HRT physiology (structure and morphology). All of these parameters have been taken into account in the approach proposed herein.

HRT deposition was carried out using the Multiple Path Particle Deposition (MPPD) v. 2.1 model (de Winter-Sorkina and Cassee, 2002). Age-specific lung geometries representing 10 distinct ages from 3 months old to 21 years old are also provided. An idealized symmetric single-path model as well as a 5-lobe symmetric multiple-path model are available for use with each age setting (Mortensen, 1983a; Mortensen, 1988; Mortensen et al., 1983b). Software inputs include morphological parameters of

pulmonary system – functional residual volume (FRC), tidal volume (TV), upper respiratory tract (URT) volume, as well as breathing frequency (BF) for each age group (*Table 4*). As MPPD results refer to a monodisperse distribution of particles, DF results are weighted by the use of volume distribution for average urban aerosols, given by Seinfeld and Pandis (2006.

Table 4. Age dependent HRT morphological parameters (de Winter-Sorkina and Cassee, 2002)

Age group	FRC (ml)	URT (ml)	BF (min^{-1})	TV (ml)
0-3 months	27.4	2.45	39	30.4
3-23 months	78.5	6.94	27	86.8
23 months-3 years	95.4	9.47	24	121
3-8 years	437	21.0	17	278
8-14 years	881	30.6	16	388
14-18 years	1935	37.4	15	447
18-21 years	1855	42.3	14	477

2.2.2.3 Cancer risk assessment

In its Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons (EPA/600/R-93/089, July 1993) and regional guidance, EPA recommends that a toxicity equivalency factor (TEF) be used to convert concentrations of carcinogenic polycyclic aromatic hydrocarbons (cPAHs) to an equivalent concentration of benzo(a)pyrene when assessing the risks posed by these substances. Calculation of the overall toxicity of the mixture of the 19 PAHs is done using Toxic Equivalent Factors (TEFs), based on the assumption that the *TEF* for B[a]P is equal to 1 (Nisbet and LaGoy, 1992).

TEQ values are calculated according to Eq. 3 using the median value of the measured concentrations, since the concentrations of individual compounds follow an asymmetric distribution:

$$TEQ = \sum_{i=1}^{19} (C_i \times TEF_i) \qquad [3]$$

Genotoxic effects of PAHs are estimated through inhalation cancer risk (*ICR*) assessment. *ICR* is expressed as a linear function of ambient *TEQ* concentration and $IUR_{B[a]P}$ (Eq. 4), as the exposure-cancer risk relationship is considered linear in the low dose region (EPA, 2005). California Environmental Protection Agency recommends an $IUR_{B[a]P}$ value of 1.1×10^{-3} $m^3/\mu g$ (CEPA, 2004).

$$ICR = TEQ \times IUR_{B[a]P} \qquad [4]$$

Equation 4 is adapted to include the exposure and dose parameters discussed earlier for each age group.

In order to calculate the risk of cancer that can be attributed to PAHs , we need to estimate the amount of *TEQ* deposited across the middle (tracheobronchial) and lower (alveoli) HRT regions (Bostrom et al., 2002). This is calculated as the sum of the products of the different size fractioned PM mass deposited across the different HRT regions, multiplied to the *TEQ* estimated for the specific size fraction.

$$TEQ_{uptake} = \sum_{1}^{n} PM_{Tr\_bronch-i} \cdot TEQ_{Tr\_bronch-i} + \sum_{1}^{n} PM_{Alveoli-i} \cdot TEQ_{Alveoli-i} \qquad [5]$$

The cancer risk function implemented is given in Equation 6, where BW_i is the average body weight of each age group and *SF* is the B[a]P slope factor, derived from the assumption that $IUR_{B[a]P}$ refers to a human of 70 kg inhaling 20 m^3 of ambient air per day. *SF* is equal to 3.85 × 10^{-6} (kg day)/ng B[a]P.

$$ICR = TEQ_{uptake} \cdot \frac{IR_i}{BW_i} \cdot SF \qquad [6]$$

2.2.3 Dioxines and furans

2.2.3.1 Rationale

Dioxines and furans (PCDDs/PCDFs) are characterized by high carcinogenic potency (Cole et al., 2003). Because PCDDs/PCDFs appears to be acting like a potent and persistent hormone agonist, it appears reasonable to incorporate mechanistic information on receptor-mediated events in risk assessments for TCDD. This information may be obtained from steroid receptor action and from molecular data on the Ah receptor (Lucier et al., 1993). This receptor based toxicity, results in sex-dependent sensitivities, as a result of a set of sex-specific PCDD/PCDF-responsive genes. However, the estimation of the additional probability of cancer due to the additional exposure burden is quite difficult (Dong et al., 2016). A major obstacle is that an elevated short term external exposure associated to the accidental event, has to be translated into long term risk estimates. Considering the significant persistence and bioaccumulation of PCDDs/PCDFs in the human body, assessing the actual internal dosimetry of this complex mixture is of particular importance. The biokinetics of TCDD are relatively well understood in adult humans (Kerger et al., 2006; Michalek and Tripathi, 1999; Milbrath et al., 2009). However, the impact of pregnancy and lactation on the elimination of TCDD and other dioxins is not clear (Emond et al., 2016). Additional insights regarding the biological perturbations induced by PCDDs/PCDFs exposure are provided by transcriptomics and metabolomics analysis, where altered levels of endogenous steroid metabolites and modified urinary bile acids profiles were identified as a result of acute exposure to PCDDs/PCDFs (Jeanneret et al., 2014). Taken together, these findings are compatible with an increased expression of cytochrome P450s, persistent hepatotoxicity, bile acid homeostasis dysregulation and oxidative stress. In *in vivo* studies (mice), serum metabolomics identified azelaic acid monoesters as significantly increased metabolites after TCDD treatment, due to downregulation of hepatic carboxylesterase 3 (CES3, also known as triglyceride hydrolase) expression in an arylhydrocarbon receptor (AhR)-dependent manner (Matsubara et al., 2012). The decreased CES3 expression was accomplished by TCDD-stimulated TGFβ-SMAD3 and IL6-STAT3 signaling, but not by direct AhR signaling, indicating that PCDDs/PCDFs affect additional pathways beyond the ones

regulated by AhR. With regard to AhR deregulation, PCDDs/PCDFs exposure elicited metabolite and gene expression changes *in vivo* subjects (mice) associated with lipid metabolism and transport, choline metabolism, bile acid metabolism, glycolysis, and glycerophospholipid metabolism (Forgacs et al., 2012). From transcriptome analysis of mitogen-induced lymphocytes cultured with 10 nM TCDD, all AhR-dependent genes were induced by 1.2- to 13-fold and plasma TCDD was associated with decreased 7-ethoxyresorufin O-deethylase activity, as well as strong positive correlation between AhR and CYP1A1/ CYP1B1 expression (Landi et al., 2003).

2.2.3.2 PCDDs/PCDFs toxicokinetics

The biokinetics of TCDD are relatively well understood in adult humans (Kerger et al., 2006; Michalek and Tripathi, 1999; Milbrath et al., 2009) and several key parameters (tissue partition coeficients and clearance rates) were used from literature. The key aspects characterizing TCDD biokinetics are very high lipophilicity (adipose:tissue blood patrition coefficient is equal to 220) and very slow elimination rate, resulting in a half-life elimination rate of 7.5 years, explaining its long persistance and bioaccumulation potential. Another important issue that needed to be addressed was the transfer of PCDDs/PCDFs through the placenta during pregnancy and maternal milk during lactation. The model describes mother fetus interactions by modelling the intra-placental properties that govern the transfer of xenobiotics and their metabolites from the mother to the fetus as it grows. The anthropometric parameters of the models are time dependent, so as to provide a lifetime internal dose assessment, as well as to describe the continuously changing physiology of the mother and the developing fetus. The model include diffusive flow from the uterus to the placenta and back during pregnancy (Beaudouin et al., 2010). Excretion via lactation is described as an output from the mammary tissue compartment through a partitioning process between mammary tissue and milk, and milk withdrawal by suckling, as described for PCBs in rats (Lee et al., 2007) and further adopted for humans (Verner et al., 2008).

2.2.3.3 Cancer risk potency

Mixtures of PCDDs/PCDFs are complex environmental mixtures of 210 interrelated chemicals composed of different dioxins and furans. For PCDD/PCDF mixtures, the reference chemical is 2,3,7,8 – tetrachlorodibenzo-p-dioxin (2,3,7,8–TCDD) because it is the most toxic and best-studied of the 210 PCDDs/PCDFs. The toxicity equivalence factor (TEF) methodology was developed by the U.S. Environmental Protection Agency to evaluate the toxicity and assess the risks of a mixture of structurally related chemicals with a common mechanism of action. A TEF is an estimate of the relative toxicity of a chemical compared to a reference chemical. Toxic Equivalents, or TEQs, are used to report the toxicity-weighted masses of mixtures of PCDDs/PCDFs. The TEQ method of PCDDs/PCDFs reporting is more meaningful than simply reporting the total number of grams of a mixture of variously toxic compounds because the TEQ method offers toxicity information about the mixture. Within the TEQ method, each PCDDs/PCDFs compound is assigned a Toxic Equivalency Factor, or TEF. This factor denotes the toxicity of a given dioxin compound relative to the toxicity of 2,3,7,8-TCDD, which is assigned the value of one. Other dioxin compounds are given equal or lower numbers, with each number roughly proportional to its toxicity relative to that of 2,3,7,8-TCDD. Developed by the World Health Organization, TEFs are used extensively by scientists and governments around the world (Van den Berg et al., 1998), finally expressing the so-called TEQ WHO (toxicity equivalent concentration in accordance with the methodology of the World Health Organization), that uses units of grams-TEQ. The EPA uses TEQ WHO to report emissions of PCDDs/PCDFs from known sources to the open

environment in its Inventory of Sources of Dioxin in the United States and similar practices have been adopted worldwide, including all the data presented in this study. To obtain the number of grams-TEQ of a dioxin mixture, one simply multiplies the mass of each compound in the mixture by its TEF and sums them up.

EPA has classified 2,3,7,8-TCDD as a Group B2, meaning a probable human carcinogen (USEPA, 1985). With regard to 2,3,7,8-TCDD, EPA has calculated an inhalation cancer slope factor of $1.5 \cdot 10^{5}$ $(mg/kg/d)^{-1}$ and an inhalation unit risk estimate of 3.3×10^{-5} $(pg/m^3)^{-1}$ for 2,3,7,8-TCDD.

2.2.4 Cadmium

2.2.4.1 Rationale

Cancer risk in occupational cohorts exposed to cadmium is limited by the insufficient number of workers that have been exposed for a long time at high levels. Moreover, the isolation of the effects of exposure to cadmium from other heavy metals (mainly arsenic and nickel) introduces more difficulties in the dissociation of the effects. However, the analyses of workers with low levels of exposure to arsenic still showed an increased lung cancer risk associated with cadmium exposure (Vimercati et al., 2017). Additional support for a cadmium-linked lung cancer risk comes from a prospective population-based study in environmentally polluted areas in Belgium (Nawrot et al., 2006). Cadmium, has been associated with prostate cancer, based on the findings from occupational cohorts exposed to cadmium, as well as studies of people residing in cadmium-contaminated areas and case–control studies, however, no consisted patern occurred among the various studies (Armstrong and Kazantzis, 1985; Sahmoun et al., 2005; Sorahan and Esmen, 2004). In any case, this hypothesis is further strengthened by a hospital-based case–control study of a highly exposed population (Vinceti et al., 2007). From case–control studies, findings indicate that also other cancer sites of the urinary trackt (kidney and bladder), but not limited to, including also breast and endometrium (Åkesson et al., 2008; Antila et al., 1996; Hu et al., 2002; Jarup et al., 1998; Kriegel et al., 2006; Pesch et al., 2000; Sorahan and Esmen, 2004). The International Agency for Research on Cancer in the most recent evaluation of the cadmium evidence for carcinogenicity in 2009, concluded once more that cadmium is carcinogenic to humans. The evidence was classified as sufficient for lung cancer and limited for prostate and kidney cancer (Straif et al., 2009).

2.2.4.2 Cadmium toxicokinetics

For the parameterization of the generic PBTK model, information on previous well validated models have been used. Cadmium has specific toxicokinetic properties, such as that cadmium metal and cadmium salts are not well absorbed; approximately 25, 1–10, or <1% of the dose is absorbed following inhalation, oral or dermal exposure. Inhalation and oral absorption can be influenced by several factors. Specifically, cadmium in cigarette smoke has a higher absorption efficiency due to its small particle size, while its absorption from the gastrointestinal tract is increased in individuals with poor iron status. After absorption from any route of exposure, cadmium widely distributes throughout the body. Animals and humans appear to have a similar pattern of distribution that is relatively independent of route of exposure, but somewhat dependent on duration of exposure. Cadmium (+2) ion does bind to anionic groups (especially sulfhydryl groups) in proteins (especially albumin and metallothionein) and other molecules (Nordberg et al., 1985), while plasma cadmium circulates primarily bound to

metallothionein and albumin (Foulkes and Blanck, 1990). It is known that cadmium does not undergo any direct metabolic reaction, such as oxidation, reduction or alkylation.

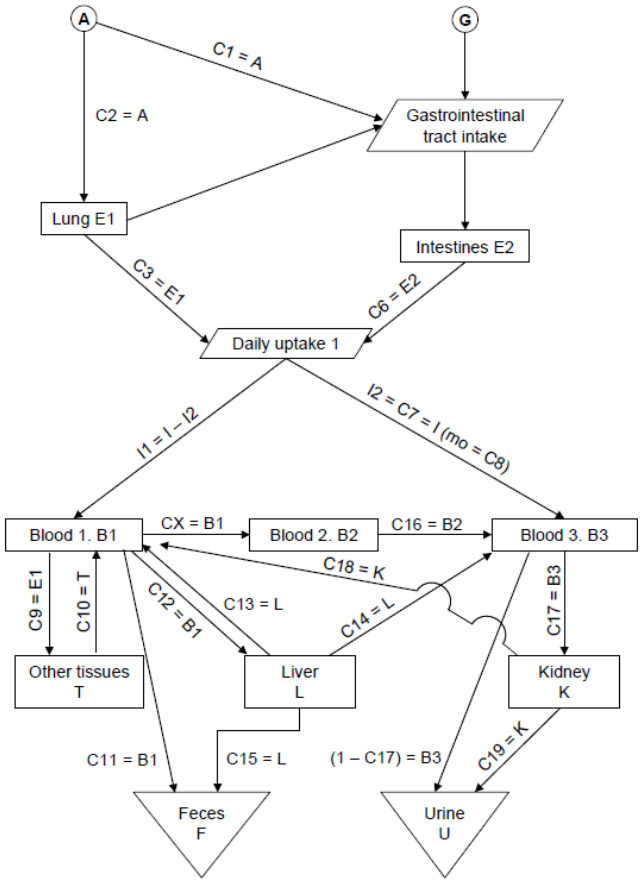

Figure 4. Conceptual PBTK model for cadmium developed by Kjellström and Nordberg (1978)

Absorbed cadmium is excreted very slowly, with urinary and fecal excretion being approximately equal, 0.007 and 0.009% of the body burden, respectively, per day (Kjellström et al., 1978). When cadmium enters human body through ingestion or inhalation, is transported to the gut via mucociliary clearance, is not absorbed and is excreted through feces. Cadmium is eliminated very slowly and the human biological half-time is above 25 years (Shaikh and Smith, 1980). Liver and kidney are tissues where cadmium is highly accumulated, followed by other tissues (mainly muscle, skin, and bone). The Nordberg-Kjellström (1978) model, illustrated in Figure 4, is a linear multi-compartment model that describes the disposition of cadmium via oral and inhalation routes of exposure. Thus, the INTEGRA generic PBPK model (Sarigiannis et al., 2014), was parameterized based on the data retrieved from the Nordberg-Kjellström (1978) model.

2.2.4.3 Cadmium cancer risk estimation

Another way to associate internal dose with cancer health effects beyond the one described above for benzene, is to use an established slope factor and to translate the intake based slope factor into a

lifetime Area Under the Curve (AUC) related cancer potency factor, defined as AUC_{SF}. Hence, the respective cancer risk (R_C), will be estimated by multiplying the actual AUC_E for a given period of time as defined by the exposure scenario, with the related unit risk UR_{SF}, that results in risk associated to 10^{-6}.

$$R_C = \frac{AUC_E}{UR_{SF}} \cdot 10^{-6}$$

The area under the curve / slope factor (UR_{SF}) is defined as the AUC that results in risk associated to 10^{-6}. This in turn is derived as follow:

- Starting from the slope factor of the respective chemical, the chronic daily intake (CDI) that results in cancer risk equal to 10^{-6} is estimated. It has to be noted that this level of environmental risc is characterized as acceptable, hence, this intake levels is now defined as CDI_{AR}.

- The CDI_{AR} is used as an input to the respective PBPK model, and the AUC for a period of 70 years is estimated; the product of this computation, describes the AUC that corresponds to a risk of 10^{-6} and is defined as UR_{SF}, since it is originally based in the initial slope factor.

This method has clear advantages, since it allows us to incorporate all key parameters that induce inter-individual variability related to physiology (e.g. bodyweight, genetic polymorphism of enzymes associated with metabolism), as well as related to the exposure scenario, such as route dependent bioavailability differences. Moreover, considering that AUC is by definition the integral of internal exposure over time, the effect of highly dynamic exposure scenarios (including short term accidental events) to internal dose fluctuations are effectively captured and incorporated in the risk calculation. This is of particular importance for compounds that are not rapidly metabolized or eliminated, where short term exposure events result in long term internal exposure changes. Up to now, the method has been effectively applied in the case of dioxins release in an accidental fire of a plastic recycling plant (Sarigiannis, 2017).

It has to be noted that cancer risk estimates derived by this method are more conservative to the ones derived by original BBDR models. BBDR models translate human epidemiological data into micro relationships, associating them with internal dose; in contrast, the AUC/slope factor association method, starts from an animal based slope factor, which is already conservative in its nature.

The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day (U.S. EPA, 1987). Since, there are no positive studies of orally ingested cadmium suitable for quantification, the quantitative estimate of carcinogenic risk from inhalation exposure was only considered. A mortality study of 292 cadmium production workers employed for a minimum of 2 years was used for estimating risks regarding respiratory and prostate cancer (Thun et al., 1985). To examine further the mortality experience of these workers, investigators from the National Institute for Occupational Safety and Health extended the study to include 602 white males with at least 6 months of production work in the same plant between 1940 and 1969. Vital status was determined through 1978, which included the addition of 5 years to the original follow-up. The unit risk should not be used if the air concentration exceeds 6 ug/m^3, since above this concentration the unit risk may not be appropriate. The data were derived from a relatively large cohort. Effects of

arsenic and smoking were accounted for in the quantitative analysis for cadmium effects. It was considered that the use of available human data was reliable because of species variations in response and the type of exposure (cadmium salt vs. cadmium fume and cadmium oxide).

For cadmium, the slope factor of 6.3 $(mg/kg/day)^{-1}$ was used for estimating the respective UR_{SF}. As a result, the respective CDI_{AR} was equal to 0.00016 µg/kg_bw/d, that was translated in an URSF of 0.18 µg*h/L. To estimate the cancer risks associated with cadmium exposure, the changes in internal dose associated with the changes in exposure were accounted for.

2.2.5 Lead

2.2.5.1 Rationale

At the moment there is a lot of evidence that children's intellectual ability is adversely affected at blood lead concentrations < 10 µg/dL (Jusko et al., 2008). To examine some of this evidence in detail, a working group was convened by the CDC, and the fifth revision of the CDC's Preventing Lead Poisoning in Young Children (CDC, 2005). The working group concluded that the "*overall weight of evidence supports an inverse association between blood lead levels < 10 µg/dL and the cognitive function of children*," with the caveat that the available data were limited by the small number of "*directly relevant cohort studies*"—studies that include multiple measures of lead exposure throughout early life and key covariate information to reduce the potential for residual confounding (CDC, 2005). Also in Europe, it has been estimated that the monetary cost in the EU associated to reduced IQ as a result of exposure only to Pb, amounts to almost 50 billion euro (Bierkens et al., 2012), since Pb, can disrupt normal development of the central nervous system, especially during fetal life and early childhood (Sarigiannis and Salifoglou, 2016).

2.2.5.2 Lead toxicokinetics

Inorganic lead is highly absorbed when inhaled, at almost 95% of the amount that was initially deposited. On the other hand, adsorption through gastrointestinal tract is greatly affected by the physiological state of the exposed individual and the species of the lead compound, as well as the presence of food. However, it has been noticed that children absorb higher levels (40–50%) of lead, than adults (3–10%). Regarding deposition, almost 94% of lead internal burden is contained in the bones and teeth versus about 73% in children (O'Flaherty, 1991). Inorganic lead presents a very long biological half-life that accounts for 30 days and 27 years for blood and bones, respectively(O'Flaherty, 1998). Lead entering human body is mainly excreted through urine and feces, independently of the route of exposure (CDC, 2007). All this information in toxicokinetics was used for parameterizing the generic PBPK model incorporated in the INTEGRA computational platform (Sarigiannis et al., 2014).

2.2.5.3 Lead neurodevelopmental disorders risk

With regard to the associated neurodevelopmental effects, it has been found (Jusko et al., 2008) that at environmentally relevant lifetime average blood lead concentration 7.2 µg/dL, was inversely associated with Full-Scale IQ ($p = 0.006$) and Performance IQ scores ($p = 0.002$). Compared with children who had lifetime average blood lead concentrations < 5 µg/dL, children with lifetime average concentrations between 5 and 9.9 µg/dL scored 4.9 points lower on Full-Scale IQ (91.3 vs. 86.4, p =

0.03). Thus, the assessment of scenarios where lead levels are going to be affected, will be based on assessment of the lead blood levels using the respective toxicokinetic model.

2.3 Noise

2.3.1 Rationale

Noise is a harmful environmental pollutant with adverse psychosocial and physiologic effects on public health (Berglund, 1999). Common psychosocial effects are annoyance and sleep disturbance (Babisch, 2005; Passchier-Vermeer and Passchier, 2000). WHO suggests that daytime and nighttime limits at 55 dB(A) and 40 dB(A) respectively, should not be exceeded in order to prevent possible such psychosocial effects (Murphy and King, 2010). Focusing on the road generated noise, it is estimated that more than 30% of the EU citizens are exposed to noise levels above those regarded as acceptable by the World Health Organization (WHO) and about 10% report severe sleep disturbance because of transportation noise at night (EEA, 2003). Furthermore, recent studies suggest that 24 million people in the European Union are highly annoyed by road traffic noise (EEA, 2000). The effects of the primary sleep disturbance include amongst other, the difficulty in falling asleep (increased sleep latency time), awakenings and alterations in the sleep stages or depth. Other primary physiological effects can also be induced by noise during sleep, including increased blood pressure, increased heart rate, increased finger pulse amplitude, vasoconstriction, change in respiration, cardiac arrhythmia and an increase in body movements. According to WHO (Berglund, 1999), exposure to night-time noise also induces secondary effects, including reduced perceived sleep quality, increased fatigue, depressed mood or well-being and decreased performance. Noise annoyance can be defined as "*a feeling of displeasure associated with any agent or condition, known or believed by an individual or group to adversely affect them*" (Lindvall & Radford 1973; Koelega 1987). However, apart from "annoyance", according to WHO (Berglund, 1999) people may feel a variety of negative emotions when exposed to community noise, and may report anger, disappointment, dissatisfaction, withdrawal, helplessness, depression, anxiety, distraction, agitation, or exhaustion . The effects of night-time annoyance are expressed in the following day, where studies have shown that people living in areas exposed to night-time noise have an increased use of sedatives or sleeping pills. Other frequently reported behavioural effects of night-time noise include closed bedroom windows and use of personal hearing protection. It is noted that sensitive groups of the above health effects include the elderly, shift workers, persons especially vulnerable to physical or mental disorders and other individuals with sleeping difficulties.

2.3.2 Noise response functions

Sleep disturbance, is classified as low, medium and high, according to the noise level the population is exposed to; it is computed via the polynomial equations 1-3 (Miedema and Vos, 2007),

$$LSD = -8.4 + 0.16*L_{night} + 0.01081*(L_{night})^2 \quad (1)$$

$$SD = 13.8 - 0.85*L_{night} + 0.01670*(L_{night})^2 \quad (2)$$

$$HSD = 20.8 - 1.05*L_{night} + 0.01486*(L_{night})^2 \quad (3)$$

where the LSD is the low sleep disturbance exposed to L_{night} in the range of 0 – 45 dB(A), SD is the sleep disturbance exposed to L_{night} in the range of 45 – 65 dB(A) and HSD is the high sleep disturbance exposed to L_{night} above 65 dB(A).

The sleep annoyance due to road transport is computed from equation 4 (Miedema and Oudshoorn, 2001),

$$HA[\%] = 0.5118*(L_{den} - 42) - 1.436*10^{-2}*(L_{den} - 42)^2 + 9.868*10^{-4}*(L_{den} - 42)^3 \quad (4)$$

where HA are the highly annoyed persons

Myocardial infraction for an L_{day} in range of 57 to 80 dB(A) is computed from the Odd Ratio presented by equation 5 and used for the calculation of the relative risk presented by equation 6 (Babisch, 2008).

$$OR = 1.63 - 6.13*10^{-4}*(L_{day},16h)^2 + 7.36*10^{-6}*(L_{day},16h)^3 \quad (5)$$

$$RR = (e^{((OR-1)/10)*(Lday,16h)} - 1) / e^{((OR-1)/10)*(Lday,16h)} * BHE * EP \quad (6)$$

Where the *BHE* is the background health effect per year i.e. 1.4 hospital admissions per 1000 population (WHO, 2011b) and *EP* is the fraction of the exposed population.

2.4 Disability adjusted life years lost (DALY)

The Disability Adjusted life Years or ***DALY*** for a disease or a health condition, are utilized defined as the sum of the Years of Life Lost (***YLL***) due to premature mortality in the population and the Years lost due disability (***YLD***) for people living with the health condition or its consequence, i.e.

DALY = YLL + YLD

Where ***YLL*** corresponds to the number of deaths multiplied by the standard life expectancy at the age at which death occurs and ***YLD*** to the number of incident cases in that period, multiplied by the average duration of the disease and a weight factor that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (dead), as defined in the following equations.

YLL = N * L

Where ***N*** is the number of deaths and L the standard life expectancy at age of death in years

YLD = I * DW * L

Where ***I*** is the number of incident cases, ***DW*** is the disability weight and ***L*** is the average duration of the case until remission or death in years.

It is noted that, for the mortality induced cases, ***DALY*** are computed solely from the ***YLL***, where as for morbidity incidences the ***YLD*** are utilized with appropriate use of a disability weight and duration of the case.

Data on severity weights for the European population, have been retrieved from the Salomon et al. (2015) study. This resulted from the combined data that have been collected from previous studies, (Salomon et al., 2012), further enhanced by a set of four new surveys, under the frame of the European disability weights measurement study (Haagsma et al., 2015). The demographic of the participants are presented in Table 5, while severity weights for selected outcomes relevant to ICARUS are presented in Table 6.

Table 5. Characteristics of the study population (Salomon et al., 2015)

	GBD 2010 web-based surveys (n=16328)	**European surveys (n=30660)**
Age (years)		
18-29	5186 (32%)	6338 (21%)
30-49	6660 (41%)	13 989 (46%)
50-69	4127 (25%)	10 333 (34%)
>70	355 (2%)	0
Unknown	0	0
Sex		
Men	5268 (32%)	14 719 (48%)
Women	11 011 (67%)	15 941 (52%)
Unknown	49 (<1%)	0
Education		
None	59 (<1%)	144 (<1%)
Primary	11 (<1%)	834 (3%)
Secondary	1035 (6%)	11 335 (37%)
Higher	15173(93%)	18 347 (60%)
Unknown	50 (<1%)	0

Table 6. Disability weights for selected health states in the Global Burden of Disease 2013 study (Salomon et al., 2015)

	Estimate
Cancer	
Cancer	
Diagnosis and primary treatment	0.288 (0.193-0.399)
Metastatic	0.451 (0.307-0.600)
Mastectomy	0.036 (0.020-0.057)
Stoma	0.095 (0.063-0.131)
Terminal phase	
With medication (for cancers and end-stage kidney or liver disease)	0.540 (0.377-0.687)
Without medication (for cancers and end-stage kidney or liver disease)	0.569 (0.389-0.727)
Cardiovascular and circulatory disease	
Acute myocardial infarction	
Days 1-2	0.432 (0.288-0.579)
Days 3-28	0.074 (0.049-0.105)
Angina pectoris	
Mild	0.033 (0.020-0.052)
Moderate	0.080 (0.052-0.113)
Severe	0.167 (0.110-0.240)
Cardiac conduction disorders and cardiac dysrhythmias	0.224 (0.151-0.312)
Claudication	0.014 (0.007-0.025)
Heart failure	
Mild	0.041 (0.026-0.062)
Moderate	0.072 (0.047-0.103)
Severe	0.179 (0.122-0.251)
Stroke	

Long-term consequences, mild	0.019 (0.010-0.032)
Long-term consequences, moderate	0.070 (0.046-0.099)
Long-term consequences, moderate, plus cognition problems	0.316 (0.206-0.437)
Long-term consequences severe	0.552 (0.377-0.707)
Long-term consequences, severe, plus cognition problems	0.588 (0.411-0.744)
Diabetes and digestive and genitourinary disease	
Diabetic foot	0.020 (0.010-0.034)
Diabetic neuropathy	0.133 (0.089-0.187)
Chronic kidney disease (stage 4)	0.104 (0.070-0.147)
End-stage renal disease	
With kidney transplantation	0.024 (0.014-0.039)
On dialysis	0.571 (0.398-0.725)
Decompensated liver cirrhosis	0.178 (0.123-0.250)
Gastric bleeding	0.325 (0.209-0.462)
Crohn's disease or ulcerative colitis	0.231 (0.156-0.320)
Benign prostatic hypertrophy: symptomatic	0.067 (0.043-0.097)
Urinary incontinence	0.139 (0.094-0.198)
Stress incontinence	0.020 (0.011-0.035)
Impotence	0.017 (0.009-0.030)
Infertility	
Primary	0.008 (0.003-0.015)
Secondary	0.005 (0.002-0.011)
Chronic respiratory disease	
Asthma	
Controlled	0.015 (0.007-0.026)
Partly controlled	0.036 (0.022-0.055)

Uncontrolled	0.133 (0.086-0.192)
Chronic obstructive pulmonary disease and other chronic respiratory diseases	
Mild	0.019 (0.011-0.033)
Moderate	0.225 (0.153-0.310)
Severe	0.408 (0.273-0.556)
Neurological disorders	
Intellectual disability	
Mild	0.043 (0.026-0.064)
Moderate	0.100 (0.066-0.142)
Severe	0.160 (0.107-0.226)
Profound	0.200 (0.133-0.283)
Motor impairment	
Mild	0.010 (0.005-0.019)
Moderate	0.061 (0.040-0.089)
Severe	0.402 (0.268-0.545)
Motor and cognitive impairments	
Mild	0.031 (0.018-0.050)
Moderate	0.203 (0.134-0.290)
Severe	0.542 (0.374-0.702)
Data in parentheses are 95% uncertainty intervals.	

Data in parentheses are 95% uncertainty intervals.

3 References

2013. European health for all database [online database]. Copenhagen, WHO Regional Office for Europe (http://data.euro.who.int/hfadb/). 2018, WHO.

Åkesson A, Julin B, Wolk A. Long-term Dietary Cadmium Intake and Postmenopausal Endometrial Cancer Incidence: A Population-Based Prospective Cohort Study. Cancer Research 2008; 68: 6435-6441.

Antila E, Mussalo-Rauhamaa H, Kantola M, Atroshi F, Westermarck T. Association of cadmium with human breast cancer. Sci Total Environ 1996; 186: 251-6.

Armitage P, Doll R. The age distribution of cancer and a multistage theory of carcinogenesis British journal of cancer 1954; 8: 1-12.

Armitage P, Doll R. A two-stage theory of carcinogenesis in relation to the age distribution of human cancer. British journal of cancer 1957; 11: 161-169.

Armstrong B, Tremblay C, Baris D, Theriault G. Lung cancer mortality and polynuclear aromatic hydrocarbons: A case- cohort study of aluminum production workers in Arvida, Quebec, Canada. American Journal of Epidemiology 1994; 139: 250-262.

Armstrong BG, Kazantzis G. Prostatic cancer and chronic respiratory and renal disease in British cadmium workers: a case control study. Br J Ind Med 1985; 42: 540-5.

ATSDR. Toxicological Profile for Carbon Monoxide. Atlanta (GA): Agency for Toxic Substances and Disease Registry (US); 2012 Jun. 3, HEALTH EFFECTS. Available from: https://www.ncbi.nlm.nih.gov/books/NBK153687/. Agency for Toxic Substances and Disease Registry, Atlanta, Georgia 30333, 2012.

Babisch W. Noise and health. Environmental Health Perspectives 2005; 113: A14-A15.

Babisch W. Road traffic noise and cardiovascular risk. Noise and Health 2008; 10: 27-33.

Beaudouin R, Micallef S, Brochot C. A stochastic whole-body physiologically based pharmacokinetic model to assess the impact of inter-individual variability on tissue dosimetry over the human lifespan. Regulatory Toxicology and Pharmacology 2010; 57: 103-116.

Berglund B. Guidelines for community noise. In: WHO, editor, New York, 1999.

Bierkens J, Buekers J, Van Holderbeke M, Torfs R. Health impact assessment and monetary valuation of IQ loss in pre-school children due to lead exposure through locally produced food. Sci Total Environ 2012; 414: 90-7.

Bostrom CE, Gerde P, Hanberg A, Jernstrom B, Johansson C, Kyrklund T, Rannug A, Tornqvist M, Victorin K, Westerholm R. Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air. Environ Health Perspect 2002; 110 Suppl 3: 451-88.

Boström CE, Gerde P, Hanberg A, Jernström B, Johansson C, Kyrklund T, Rannug A, Törnqvist M, Victorin K, Westerholm R. Cancer risk assessment, indicators, and guidelines for polycyclic aromatic hydrocarbons in the ambient air. Environmental Health Perspectives 2002; 110: 451-488.

CDC. Preventing Lead Poisoning in Young Children: A Statement by the Centers for Disease Control and Prevention. 5th Revision. Atlanta, GA:Centers for Disease

Control and Prevention. Available: http://www.cdc.gov/nceh/lead/publications/PrevLeadPoisoning.pdf, 2005.

CDC. ToxGuide for Lead (Pb), 2007.

CEPA. The Report on Diesel Exhaust, 2004.

Chen CW. Armitage-Doll two-stage model: Implications and extension. Risk Analysis 1993; 13: 273-280.

Cole P, Trichopoulos D, Pastides H, Starr T, Mandel JS. Dioxin and cancer: a critical review. Regul Toxicol Pharmacol 2003; 38: 378-88.

Cox Jr LA. Reassessing benzene risks using internal doses and Monte-Carlo uncertainty analysis. Environmental Health Perspectives 1996; 104: 1413-1429.

Crump KS. Risk of benzene-induced leukemia: A sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates. Journal of Toxicology and Environmental Health 1994; 42: 219-242.

Crump KS, Allen BC. Quantitative Estimates of the Risk of Leukemia from Occupational Exposures to Benzene. Final Report to the Occupational Safety and Health Administration. LA:Science Research Systems, Ruston 1984.

de Winter-Sorkina R, Cassee FR. From concentration to dose: factors influencing airborne particulate matter deposition in humans and rats. RIVM National Institute for Public Health and the Environment, Bilthoven, 2002.

Dong Z, Yuan G, Hu J. Uncertainty analysis in 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) cancer dose-response for three occupational cohorts. Environ Int 2016; 88: 53-9.

Dvorská A, Komprdová K, Lammel G, Klánová J, Plachá H. Polycyclic aromatic hydrocarbons in background air in central Europe – Seasonal levels and limitations for source apportionment. Atmospheric Environment 2012; 46: 147-154.

EEA. Are we moving in the right direction? Indicators on transport and environmental integration in the EU:TERM 2000. Indicator 4: Traffic noise: exposure and annoyance. Environmental issue report, 2000.

EEA. Europe's environment: The third assessment. EEA Environmental Assessment. Report No. 10, Copenhagen, 2003.

Emond C, DeVito M, Warner M, Eskenazi B, Mocarelli P, Birnbaum LS. An assessment of dioxin exposure across gestation and lactation using a PBPK model and new data from Seveso. Environ Int 2016; 92-93: 23-32.

EPA US. Guidelines for Carcinogen Risk Assessment, Washington, DC, 2005.

EU. Directive 2000/69/EC of the European Parliament and of the Council of 16 November 2000 relating to limit values for benzene and carbon monoxide in ambient air, 2000.

EU. Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe, 2008.

EUROSTAT. Population data, 2011.

Forgacs AL, Kent MN, Makley MK, Mets B, DelRaso N, Jahns GL, Burgoon LD, Zacharewski TR, Reo NV. Comparative metabolomic and genomic analyses of TCDD-elicited metabolic disruption in mouse and rat liver. Toxicol Sci 2012; 125: 41-55.

Foulkes EC, Blanck S. Acute cadmium uptake by rabbit kidneys: mechanism and effects. Toxicol Appl Pharmacol 1990; 102: 464-73.

Freeman DJ, Cattell FCR. Woodburning as a source of atmospheric polycyclic aromatic hydrocarbons. Environmental Science & Technology 1990; 24: 1581-1585.

Haagsma JA, Maertens de Noordhout C, Polinder S, Vos T, Havelaar AH, Cassini A, Devleesschauwer B, Kretzschmar ME, Speybroeck N, Salomon JA. Assessing disability weights based on the responses of 30,660 people from four European countries. Population Health Metrics 2015; 13: 10.

Hoek G, Pattenden S, Willers S, Antova T, Fabianova E, Braun-Fahrlander C, Forastiere F, Gehring U, Luttmann-Gibson H, Grize L, Heinrich J, Houthuijs D, Janssen N, Katsnelson B, Kosheleva A, Moshammer H, Neuberger M, Privalova L, Rudnai P, Speizer F, Slachtova H, Tomaskova H, Zlotkowska R, Fletcher T. PM10, and children's respiratory symptoms and lung function in the PATY study. Eur Respir J 2012; 40: 538-47.

Hu J, Mao Y, White K. Renal cell carcinoma and occupational exposure to chemicals in Canada. Occup Med (Lond) 2002; 52: 157-64.

Hurley F, Hunt A, Cowie H, Holland M, Miller B, Pye S, Watkiss P. Methodology for the cost-benefit analysis for CAFE: Volume 2: Health impact assessment. In: IOM, editor. IOM, Edinburg, 2005.

IARC. Some non-heterocyclic polycyclic aromatic hydrocarbons and some related exposures. IARC Monogr Eval Carcinog Risks Hum. 92, 2010, pp. 1-853.

IOM. Final report on risk functions used in the case studies. In: IOM, editor. IOM, Edinburg, 2011.

Janssen NAH, Hoek G, Simic-Lawson M, Fischer P, van Bree L, ten Brink H, Keuken M, Atkinson RW, Anderson HR, Brunekreef B, Cassee FR. Black Carbon as an Additional Indicator of the Adverse Health Effects of Airborne Particles Compared with PM(10) and PM(2.5). Environmental Health Perspectives 2011; 119: 1691-1699.

Jarup L, Bellander T, Hogstedt C, Spang G. Mortality and cancer incidence in Swedish battery workers exposed to cadmium and nickel. Occupational and Environmental Medicine 1998; 55: 755-759.

Jeanneret F, Boccard J, Badoud F, Sorg O, Tonoli D, Pelclova D, Vlckova S, Rutledge DN, Samer CF, Hochstrasser D, Saurat J-H, Rudaz S. Human urinary biomarkers of dioxin exposure: Analysis by metabolomics and biologically driven data dimensionality reduction. Toxicology Letters 2014; 230: 234-243.

Jusko TA, Henderson CR, Lanphear BP, Cory-Slechta DA, Parsons PJ, Canfield RL. Blood lead concentrations < 10 microg/dL and child intelligence at 6 years of age. Environ Health Perspect 2008; 116: 243-8.

Karakitsios SP, Delis VK, Kassomenos PA, Pilidis GA. Contribution to ambient benzene concentrations in the vicinity of petrol stations: Estimation of the associated health risk. Atmospheric Environment 2007; 41: 1889-1902.

Karakitsios SP, Kassomenos PA, Sarigiannis DA, Pilidis GA. Exposure modeling of benzene exploiting passive-active sampling data. Environmental Modeling and Assessment 2010; 15: 283-294.

Kennedy IM. The health effects of combustion-generated aerosols. Proceedings of the Combustion Institute 2007; 31: 2757-2770.

Kerger BD, Leung H-W, Scott P, Paustenbach DJ, Needham LL, Patterson DG, Gerthoux PM, Mocarelli P. Age- and Concentration-Dependent Elimination Half-Life of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in Seveso Children. Environmental Health Perspectives 2006; 114: 1596-1602.

Kjellström T, Borg K, Lind B. Cadmium in feces as an estimator of daily cadmium intake in Sweden. Environmental Research 1978; 15: 242-251.

Kjellström T, Nordberg GF. A kinetic model of cadmium metabolism in the human being. Environmental Research 1978; 16: 248-269.

Knudson Jr AG. Mutation and cancer: statistical study of retinoblastoma. Proceedings of the National Academy of Sciences of the United States of America 1971; 68: 820-823.

Kriegel AM, Soliman AS, Zhang Q, El-Ghawalby N, Ezzat F, Soultan A, Abdel-Wahab M, Fathy O, Ebidi G, Bassiouni N, Hamilton SR, Abbruzzese JL, Lacey MR, Blake DA. Serum cadmium levels in pancreatic cancer patients from the East Nile Delta region of Egypt. Environ Health Perspect 2006; 114: 113-9.

Lai CK, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 2009; 64: 476-83.

Lai HK, Jantunen MJ, Kunzli N, Kulinskaya E, Colvile R, Nieuwenhuijsen MJ. Determinants of indoor benzene in Europe. Atmospheric Environment 2007; 41: 9128-9135.

Landi MT, Bertazzi PA, Baccarelli A, Consonni D, Masten S, Lucier G, Mocarelli P, Needham L, Caporaso N, Grassman J. TCDD-mediated alterations in the AhR-dependent pathway in Seveso, Italy, 20 years after the accident. Carcinogenesis 2003; 24: 673-80.

Lee SK, Ou YC, Andersen ME, Yang RSH. A physiologically based pharmacokinetic model for lactational transfer of PCB 153 with or without PCB 126 in mice. Archives of Toxicology 2007; 81: 101-111.

Lin CC, Chen SJ, Huang KL, Lee WJ, Lin WY, Tsai JH, Chaung HC. PAHs, PAH-induced carcinogenic potency, and particle-extract-induced cytotoxicity of traffic-related nano/ultrafine particles. Environmental Science and Technology 2008; 42: 4229-4235.

Lucier GW, Portier CJ, Gallo MA. Receptor mechanisms and dose-response models for the effects of dioxins. Environ Health Perspect 1993; 101: 36-44.

Manning CC, Schlosser PM, Tran HT. A multicompartment liver-based pharmacokinetic model for benzene and its metabolites in mice. Bulletin of Mathematical Biology 2010; 72: 507-540.

Masclet P, Bresson MA, Mouvier G. Polycyclic aromatic hydrocarbons emitted by power stations, and influence of combustion conditions. Fuel 1987; 66: 556-562.

Matsubara T, Tanaka N, Krausz KW, Manna SK, Kang DW, Anderson ER, Luecke H, Patterson AD, Shah YM, Gonzalez FJ. Metabolomics identifies an inflammatory cascade involved in dioxin- and diet-induced steatohepatitis. Cell Metab 2012; 16: 634-44.

McConnell R, Berhane K, Gilliland F, Molitor J, Thomas D, Lurmann F, Avol E, Gauderman WJ, Peters JM. Prospective study of air pollution and bronchitic symptoms in children with asthma. Am J Respir Crit Care Med 2003; 168: 790-7.

Michalek JE, Tripathi RC. Pharmacokinetics of TCDD in veterans of Operation Ranch Hand: 15-year follow-up. J Toxicol Environ Health A 1999; 57: 369-78.

Miedema HME, Oudshoorn CGM. Annoyance from transportation noise: Relationships with exposure metrics DNL and DENL and their confidence intervals. Environmental Health Perspectives 2001; 109: 409-416.

Miedema HME, Vos H. Associations between self-reported sleep disturbance and environmental noise based on reanalyses of pooled data from 24 studies. Behavioral Sleep Medicine 2007; 5: 1-20.

Migliore E, Berti G, Galassi C, Pearce N, Forastiere F, Calabrese R, Armenio L, Biggeri A, Bisanti L, Bugiani M, Cadum E, Chellini E, Dell'orco V, Giannella G, Sestini P, Corbo G, Pistelli R, Viegi G, Ciccone G. Respiratory symptoms in children living near busy roads and their relationship to vehicular traffic: results of an Italian multicenter study (SIDRIA 2). Environ Health 2009; 8: 27.

Milbrath MO, Wenger Y, Chang CW, Emond C, Garabrant D, Gillespie BW, Jolliet O. Apparent half-lives of dioxins, furans, and polychlorinated biphenyls as a function of age, body fat, smoking status, and breast-feeding. Environ Health Perspect 2009; 117: 417-25.

Moolgavkar SH. The multistage theory of carcinogenesis and the age distribution of cancer in man. Journal of the National Cancer Institute 1978; 61: 49-52.

Moolgavkar SH, Knudson Jr AG. Mutation and cancer: A model for human carcinogenesis. Journal of the National Cancer Institute 1981; 66: 1037-1052.

Moolgavkar SH, Venzon DJ. Two-event models for carcinogenesis: Incidence curves for childhood and adult tumors. Mathematical Biosciences 1979; 47: 55-77.

Mortensen JD. A Study of Age Specific Human Respiratory Morphometry: Final Report: UBTL Division, University of Utah Research Institute, 1983a.

Mortensen JD, et al. Age related morphometric analysis of human lung casts. Extrapolation of Dosimetric Relationships for Inhaled Particles and Gases. San Diego, CA.: Academic Press., 1988.

Mortensen JD, Young JD, Stout L, Stout A, Bagley B, Schaap RN. A numerical identification system for airways in the lung. Anatomical Record 1983b; 206: 103-114.

Murphy E, King EA. Strategic environmental noise mapping: Methodological issues concerning the implementation of the EU Environmental Noise Directive and their policy implications. Environment International 2010; 36: 290-298.

Nawrot T, Plusquin M, Hogervorst J, Roels HA, Celis H, Thijs L, Vangronsveld J, Van Hecke E, Staessen JA. Environmental exposure to cadmium and risk of cancer: a prospective population-based study. The Lancet Oncology 2006; 7: 119-126.

Nielsen T. Traffic contribution of polycyclic aromatic hydrocarbons in the center of a large city. Atmospheric Environment 1996; 30: 3481-3490.

Nisbet ICT, LaGoy PK. Toxic equivalency factors (TEFs) for polycyclic aromatic hydrocarbons (PAHs). Regulatory Toxicology and Pharmacology 1992; 16: 290-300.

Nordberg GF, Kjellström T, Nordberg M. Kinetics and metabolism. In: Friberg L, Elinder CG, Kjellström T, et al. eds. Cadmium and health: A toxicological and epidemiological appraisal. Vol. I. Exposure, dose, and metabolism. Boca Raton, FL: CRC Press, 103-178., 1985.

Nordling CO. A new theory on cancer-inducing mechanism. British journal of cancer 1953; 7: 68-72.

O'Flaherty EJ. Physiologically based models for bone-seeking elements: III. Human skeletal and bone growth. Toxicology and Applied Pharmacology 1991; 111: 332-341.

O'Flaherty EJ. A physiologically based kinetic model for lead in children and adults. Environmental Health Perspectives 1998; 106: 1495-1503.

Ostro BD, Rothschild S. Air pollution and acute respiratory morbidity: an observational study of multiple pollutants. Environ Res 1989; 50: 238-47.

Passchier-Vermeer W, Passchier WF. Noise exposure and public health. Environmental Health Perspectives 2000; 108: 123-131.

Pekari K, Vainiotalo S, Heikkila P, Palotie A, Luotamo M, Riihimaki V. Biological monitoring of occupational exposure to low levels of benzene. Scandinavian Journal of Work, Environment and Health 1992; 18: 317-322.

Perbellini L, Faccini GB, Pasini F, Cazzoli F, Pistoia S, Rosellini R, Valsecchi M, Brugnone F. Environmental and occupational exposure to benzene by analysis of breath and blood. British Journal of Industrial Medicine 1988; 45: 345-352.

Pesch B, Haerting J, Ranft U, Klimpel A, Oelschlagel B, Schill W. Occupational risk factors for renal cell carcinoma: agent-specific results from a case-control study in Germany. MURC Study Group. Multicenter urothelial and renal cancer study. Int J Epidemiol 2000; 29: 1014-24.

Pope Iii CA, Dockery DW. Health effects of fine particulate air pollution: Lines that connect. Journal of the Air and Waste Management Association 2006; 56: 709-742.

Rinsky RA, Smith AB, Hornung R. Benzene and leukemia. An epidemiologic risk assessment. New England Journal of Medicine 1987a; 316: 1044-1050.

Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ. Benzene and Leukemia. New England Journal of Medicine 1987b; 316: 1044-1050.

Rinsky RA, Young RJ, Smith AB. Leukemia in benzene workers. American Journal of Industrial Medicine 1981; 2: 217-245.

Sahmoun AE, Case LD, Jackson SA, Schwartz GG. Cadmium and Prostate Cancer: A Critical Epidemiologic Analysis. Cancer Investigation 2005; 23: 256-263.

Salomon JA, Haagsma JA, Davis A, de Noordhout CM, Polinder S, Havelaar AH, Cassini A, Devleesschauwer B, Kretzschmar M, Speybroeck N, Murray CJL, Vos T. Disability weights for the Global Burden of Disease 2013 study. The Lancet Global Health 2015; 3: e712-e723.

Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, Begum N, Shah R, Karyana M, Kosen S, Farje MR, Moncada G, Dutta A, Sazawal S, Dyer A, Seiler J, Aboyans V, Baker L, Baxter A, Benjamin EJ, Bhalla K, Bin Abdulhak A, Blyth F, Bourne R, Braithwaite T, Brooks P, Brugha TS, Bryan-Hancock C, Buchbinder R, Burney P, Calabria B, Chen H, Chugh SS, Cooley R, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, Davis A, Degenhardt L, Diaz-Torne C, Dorsey ER, Driscoll T, Edmond K, Elbaz A, Ezzati M, Feigin V, Ferri CP, Flaxman AD, Flood L, Fransen M, Fuse K, Gabbe BJ, Gillum RF, Haagsma J, Harrison JE, Havmoeller R, Hay RJ, Hel-Baqui A, Hoek HW, Hoffman H, Hogeland E, Hoy D, Jarvis D, Karthikeyan G, Knowlton LM, Lathlean T, Leasher JL, Lim SS, Lipshultz SE, Lopez AD, Lozano R, Lyons R, Malekzadeh R, Marcenes W, March L, Margolis DJ, McGill N, McGrath J, Mensah GA, Meyer AC, Michaud C, Moran A, Mori R, Murdoch ME, Naldi L, Newton CR, Norman R, Omer SB, Osborne R, Pearce N, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Pourmalek F, Prince M, Rehm JT, Remuzzi G, Richardson K, Room R, Saha S, Sampson U, Sanchez-Riera L, Segui-Gomez M, Shahraz S, Shibuya K, Singh D, Sliwa K, Smith E, Soerjomataram I, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Taylor HR, Tleyjeh IM, van der Werf MJ, Watson WL, Weatherall DJ, Weintraub R, Weisskopf MG, Whiteford H, Wilkinson JD, Woolf AD, Zheng ZJ, Murray CJ, Jonas JB. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2129-43.

Samoli E, Touloumi G, Schwartz J, Anderson HR, Schindler C, Forsberg B, Vigotti MA, Vonk J, Košnik M, Skorkovsky J, Katsouyanni K. Short-term effects of carbon monoxide on mortality: An analysis within the APHEA project. Environmental Health Perspectives 2007; 115: 1578-1583.

Sarigiannis D, Karakitsios S, Gotti A, Loizou G, Cherrie J, Smolders R, De Brouwere K, Galea K, Jones K, Handakas E, Papadaki K, Sleeuwenhoek A. Integra: From global scale contamination to tissue dose. Proceedings - 7th International Congress on Environmental Modelling and Software: Bold Visions for Environmental Modeling, iEMSs 2014. 2, 2014, pp. 1001-1008.

Sarigiannis DA. Assessing the impact of hazardous waste on children's health: The exposome paradigm. Environ Res 2017; 158: 531-541.

Sarigiannis DA, Gotti A. Biology-based dose-response models for health risk assessment of chemical mixtures. Fresenius Environmental Bulletin 2008; 17: 1439-1451.

Sarigiannis DA, Salifoglou A. Research directives toward deciphering adverse outcome pathways induced by environmental metallotoxins. Current Opinion in Chemical Engineering 2016; 13: 161-169.

Sarigiannis DA, Karakitsios SP, Kermenidou MV. Health impact and monetary cost of exposure to particulate matter emitted from biomass burning in large cities. Science of The Total Environment 2015; 524-525: 319-330.

Schindler C, Keidel D, Gerbase MW, Zemp E, Bettschart R, Brandli O, Brutsche MH, Burdet L, Karrer W, Knopfli B, Pons M, Rapp R, Bayer-Oglesby L, Kunzli N, Schwartz J, Liu L-JS, Ackermann-Liebrich U, Rochat T, the SAPALDIA Team. Improvements in PM10 Exposure and Reduced Rates of Respiratory Symptoms in a Cohort of Swiss Adults (SAPALDIA). Am. J. Respir. Crit. Care Med. 2009; 179: 579-587.

Schöllnberger H, Manuguerra M, Bijwaard H, Boshuizen H, Altenburg HP, Rispens SM, Brugmans MJP, Vineis P. Analysis of epidemiological cohort data on smoking effects and lung cancer with a multi-stage cancer model. Carcinogenesis 2006; 27: 1432-1444.

Seinfeld JH, Pandis SN. Atmospheric Chemistry and Physics: From Air Pollution to Climate Change. New York, NY, 2006.

Shaikh ZA, Smith JC. Metabolism of orally ingested cadmium in humans. In: Holmstedt B, Lauwerys R, Mercier M, et al., eds. Mechanisms of toxicity and hazard evaluation. New York, NY: Elservier/North-Holland Biomedical Press, 569-574. 1980.

Sorahan T, Esmen NA. Lung cancer mortality in UK nickel-cadmium battery workers, 1947–2000. Occupational and Environmental Medicine 2004; 61: 108-116.

Stocks P. A study of the age curve for cancer of the stomach in connection with a theory of the cancer producing mechanism. British journal of cancer 1953; 7: 407- 417.

Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Guha N, Freeman C, Galichet L, Cogliano V. A review of human carcinogens--Part C: metals, arsenic, dusts, and fibres. Lancet Oncol 2009; 10: 453-4.

Tan WY. Stochastic Models of Carcinogenesis. New York, 1991.

Tardif R, Charest-Tardif G, Brodeur J, Krishnan K. Physiologically based pharmacokinetic modeling of a ternary mixture of alkyl benzenes in rats and humans. Toxicology and Applied Pharmacology 1997; 144: 120-134.

Thun MJ, Schnorr TM, Smith AB, Halperin WE, Lemen RA. Mortality among a cohort of U.S. cadmium production workers--an update. J Natl Cancer Inst 1985; 74: 325-33.

U.S. EPA. Integrated Risk Information System (IRIS). Chemical Assessment Summary. Cadmium, 1987.

USEPA. U.S. Environmental Protection Agency. Health Assessment Document for Polychlorinated Dibenzo-p-Dioxin. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, Cincinnati, OH. EPA 600/8-84-014F. 1985, 1985.

USEPA. Supplementary guidance for conducting health risk assessment of chemical mixtures. Risk Assessment Forum, Washington D.C. , 2000.

Van den Berg M, Birnbaum L, Bosveld AT, Brunstrom B, Cook P, Feeley M, Giesy JP, Hanberg A, Hasegawa R, Kennedy SW, Kubiak T, Larsen JC, van Leeuwen FX, Liem AK, Nolt C, Peterson RE, Poellinger L, Safe S, Schrenk D, Tillitt D, Tysklind M, Younes M, Waern F, Zacharewski T. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environ Health Perspect 1998; 106: 775-92.

Venkataraman C, Lyons JM, Friedlander SK. Size distributions of polycyclic aromatic hydrocarbons and elemental carbon. 1. Sampling, measurement methods, and source characterization. Environmental Science Technology 1994; 28: 555-562.

Verner MA, Charbonneau M, Lopez-Carrillo L, Haddad S. Physiologically based pharmacokinetic modeling of persistent organic pollutants for lifetime exposure assessment: A new tool in breast cancer epidemiologic studies. Environmental Health Perspectives 2008; 116: 886-892.

Vimercati L, Gatti MF, Gagliardi T, Cuccaro F, De Maria L, Caputi A, Quarato M, Baldassarre A. Environmental exposure to arsenic and chromium in an industrial area. Environmental Science and Pollution Research 2017; 24: 11528-11535.

Vinceti M, Venturelli M, Sighinolfi C, Trerotoli P, Bonvicini F, Ferrari A, Bianchi G, Serio G, Bergomi M, Vivoli G. Case-control study of toenail cadmium and prostate cancer risk in Italy. Science of The Total Environment 2007; 373: 77-81.

Waidyanatha S, Rothman N, Li G, Smith MT, Yin S, Rappaport SM. Rapid determination of six urinary benzene metabolites in occupationally exposed and unexposed subjects. Analytical Biochemistry 2004; 327: 184-199.

WHO. Outdoor air pollution - Assessing the environmental burden of disease at national and local levels. Environmental Burden of Disease Series, No. 5, Geneva, 2004.

WHO. Health relevance of particulate matter from various sources. In: WHO, editor. Report on a WHO workshop Bonn, Germany 26–27 March 2007, 2007.

WHO. THE GLOBAL BURDEN OF DISEASE. In: WHO, editor, Geneva, 2008.

WHO. Burden of disease from environmental noise. WHO Regional Office for Europe, Copenhagen, 2011b.

WHO. European hospital morbidity database [web site]. Copenhagen, WHO Regional Office for Europe (http://www.euro.who.int/en/what-we-do/data-andevidence/databases/european-hospital-morbidity-database-hmdb2. 2018, 2013a.

WHO. European mortality database (MDB) [online database]. Copenhagen, WHO Regional Office for Europe (http://data.euro.who.int/hfamdb/. 2018, 2013b.

WHO. 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. WHO Regional Office for Europe, Copenhagen, Denmark, 2013c.

WHO. WHO methods for life expectancy and healthy life expectancy. In: Systems DoHSaI, editor. Global Health Estimates Technical Paper WHO/HIS/HSI/GHE/2014.5, Geneva, Switzerland, 2014.

Wiriya W, Prapamontol T, Chantara S. PM10-bound polycyclic aromatic hydrocarbons in Chiang Mai (Thailand): Seasonal variations, source identification, health risk assessment and their relationship to air-mass movement. Atmospheric Research 2013; 124: 109-122.

Wong O. An industry wide mortality study of chemical workers occupationally exposed to benzene. I. General results. British Journal of Industrial Medicine 1987; 44: 365-381.

Yokley K, Tran HT, Pekari K, Rappaport S, Riihimaki V, Rothman N, Waidyanatha S, Schlosser PM. Physiologically-based pharmacokinetic modeling of benzene in humans: A Bayesian approach. Risk Analysis 2006; 26: 925-943.

Yu Y, Guo H, Liu Y, Huang K, Wang Z, Zhan X. Mixed uncertainty analysis of polycyclic aromatic hydrocarbon inhalation and risk assessment in ambient air of Beijing. Journal of Environmental Sciences 2008; 20: 505-512.

Zhang K, Zhang B-Z, Li S-M, Wong CS, Zeng EY. Calculated respiratory exposure to indoor size-fractioned polycyclic aromatic hydrocarbons in an urban environment. Science of The Total Environment 2012; 431: 245-251.