Costs of Health Damage from Atmospheric Emissions of Toxic Metals
Part 2: Analysis for Arsenic and Cadmium

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Abstract

In this part of the series we explain the detailed literature review and calculations for the calculation of impacts and damage costs of arsenic and cadmium. Methodology and general assumptions are explained in the companion paper, part 1 of this series. For arsenic the damage cost is 3,742 €$_{2010}$/kg; about 38% is due to mortality, the rest from loss of IQ points, chronic bronchitis, diabetes and non-fatal cancers. For cadmium the damage cost is 92,820 €$_{2010}$/kg, about 98% due to mortality and the rest due to non-fatal cancers and osteoporosis. These costs are per kg of emitted pollutant. The spreadsheet with the calculations can be found at http://www.arirabl.org/software/ [1].

1. Arsenic

1.1. General Considerations

Arsenic is a well known poison. Exposure to As in drinking water increases the risk of cancer of lung, skin, bladder and kidney; there is also strong evidence for hypertension and cardiovascular disease WHO [2001]. More recent studies have also found associations with intellectual function, respiratory impacts, diabetes, infant mortality and general mortality that we find sufficiently convincing for consideration. Yoshida and Yamauchi [2004] provide a review of RRs.

Here we consider only the exposure to inorganic As, since organic As is far less toxic. Atmospheric emissions, from volcanoes or combustion, are inorganic, as is As in drinking water. For food, by contrast, the available data indicate that only about 25% of the As is inorganic [WHO 2001]. Since the epidemiological studies are based on As in water rather than As in food, we base our calculations on the water dose but then multiply by a factor

$$\text{Total dose/dose from water} = (31.1 + 3.9 + 275*0.25)/31.1 = 3.3, \quad (1)$$

[1] Because of rounding, the multiplication of the some of the numbers in this paper differs slightly from the stated results.

assuming that all inorganic As is equally toxic, 31.1, 3.9 and 275 mg per emitted kg being the intake fractions for drinking water, inhalation and food, respectively, as per Table 1 of Part 1. To relate drinking water concentration to intake we take an average consumption of 0.6 m^3/yr as per Spadaro and Rabl [2004], implying

$$\text{annual intake per } (\mu g_{As}/L) = 0.60\ (mg_{As}/yr)/(\mu g_{As}/L). \quad (2)$$

A significant amount of As is of natural origin: volcanoes contribute atmospheric emissions and in some regions rivers or ground water contain high levels of As because of their geology. There has been some debate about the possibility that As might be an essential element for the human body [Nielsen 1996]; however, people would in any case receive adequate quantities of organic As from food, even if air emissions due to combustion were eliminated. Therefore we proceed on the assumption that air emissions are entirely harmful.

1.2. Non-cancer Mortality

Several studies have observed significant increases in non-cancer mortality, either as increase in general mortality [Wade et al 2009, Sohel et al 2009, Argos et al 2010] or in cardiovascular mortality [Chen et al 1996, Chen et al 2011, Yuan et al 2007]. For general mortality the cohort studies of Sohel et al and Argos et al are quite similar: both looked at populations in Bangladesh and examined the relation between mortality and long term exposure to As in the water supply. Exposure to As was the result of installing water wells to replace the bacteria-infected surface water that had been used before. Sohel et al had a sample size of 121,123 persons with follow-up from 1991 to 2000, whereas Argos et al had a much smaller sample, 11,746 persons, with follow-up from 2000 to 2009. Since the concentration intervals are sufficiently similar we tried to combine their RR numbers in a linear regression, using the usual weighting in proportion to the inverse of the squared standard errors. The resulting RR are very close to those of Sohel et al because their confidence intervals are much more narrow, not surprising in view of their much larger study population. Therefore we decided to use only the results of Sohel et al.

Fitting a straight line to the data of Sohel et al, constrained to RR = 1 at the lowest As concentration, we obtain this relation between ΔRR and concentration increment in the water supply

$$\Delta RR/\Delta conc = 0.0013/(\mu g_{As}/L) \quad . \quad (3)$$

For comparison we also look at the study of Wade et al [2009] in Inner Mongolia where As pollution resulted when shallow wells were replaced by deep wells, similar to what happened in Bangladesh and at about the same time. From Table 2 of Wade et al we extract an estimate of $\Delta RR/\Delta conc = 0.002/(\mu g_{As}/L)$ for exposures longer than ten years, not too different from Eq.3. But we prefer Sohel et al because of the much larger number of deaths (9015 compared to 572 in Wade et al).

Multiplying Eq.3 by Eq.2 of Part 1 for the LE loss per ΔRR of mortality risk and dividing by 0.6 $(mg_{As}/yr)/(\mu g_{As}/L)$ as per Eq.2 for the relation between As intake and concentration in the water supply we obtain the ERF slope as

$$s_{ERF} = [0.0013/(\mu g_{As}/L)] * [0.148 \text{ YOLL/yr per } \Delta RR]/[0.60 (mg_{As}/yr)/(\mu g_{As}/L)] \quad (4)$$
$$= 0.00032 (YOLL/yr)/(mg_{As}/yr) \quad .$$

With the IF from water consumption, 31.1 mg_{As}/kg_{As} according to Table 1 of Part 1, this implies an LE loss of 0.0099 $YOLL/kg_{As}$. Multiplying by VOLY, as well as the factor 3.3 of Eq.1 to account for all inorganic As, we obtain a mortality damage cost of 2,788 $€/kg_{As}$. However, the question of double counting arises when adding this to the cost of fatal cancers of Section 2.2. To avoid double counting, we note that the study of Sohel et al involves a mean exposure duration of 13 yr, not long enough for most cancers to develop and become fatal. That is also the case for Argos et al and Wade et al. Sohel et al; the latter provide (in their Erratum) a breakdown by causes of death, and cancers account only for 589 of the 9015 deaths in their data set. Therefore we further multiply the 2,788 $€/kg_{As}$ by (1 - 589/9015) to obtain a number that can be added to the cost of fatal cancers, namely 2,606 $€_{2010}/kg_{As}$, without discounting or threshold.

We have checked (details not shown here) that this result is compatible, in view of the uncertainties, with the results for cardiovascular mortality provided by Chen et al 1996, Chen et al 2011 and Yuan et al 2007. As another test we have looked at the impact of As on hypertension as observed by Rahman et al [1999] and Chen et al [1995]. Increased hypertension has also been observed by Mordukhovich et al [2012] but we cannot use their results because they are based on As in toenails, a biomarker for which we have no conversion to intake. Combining the RR of Rahman et al and of Chen et al for the increase of hypertension due to As in drinking water with the relation between hypertension and mortality of Franco et al [2005], we find a mortality impact similar to the cardiovascular mortality of Chen et al 1996, Chen et al 2011 and Yuan et al 2007 (details not shown here).

1.3. Cancers

The link between As inhalation and lung cancer has been established by numerous studies, especially of workers in the metals industries, see references in the IRIS web site for inorganic As. The IRIS web site for As (not updated since 1993) shows Air Unit Risk = 4.30E-03 lung cancers per ($\mu g_{As}/m^3$). More recently Lubin et al [2008] present clear evidence for lung cancers due to inhaled As and provide an ERF. The IRIS web site also indicates a unit risk factor for skin cancer due to intake from water. However, here we chose an alternative approach for all cancers, based on Smith et al [1998]. Even though the latter is based on As in water only, we extend the results to all intake of inorganic As, because Smith et al [2009] have shown that the lung cancer risk (by far the dominant cancer for As) is the same whether As is inhaled or ingested, if the absorbed dose is measured as urinary As concentration.

Whereas the causality is well established for lung and skin cancer, there has been some debate about bladder, kidney and liver cancer. The review by Mink et al [2008] and the study by Meliker et al [2010] did not find persuasive evidence for bladder cancer; however, that may be due to a longer than expected latency period [Bates et al 2004]. Kurttio et al [1999] and Smith et al [1998] do find significant associations for bladder cancer, and Yuan et al [2010] and Hopenhayn-Rich [1998] find significant associations with kidney cancer.

On balance, we believe that the best and most comprehensive data for cancer mortality due to As can be found in Smith et al [1998] because it involves a very large population, 421,000

persons in Chile, that was exposed for several decades to high concentrations in their water supply. In part a) of Table 1 we show the key results of Smith et al [1998] for observed and expected cancer deaths in 1991 (their Tables 2 and 3). The standard mortality ratios (SMR) are the ratio of observed and expected deaths, and they are very significant for cancers of bladder, kidney, lung and skin. In part b) of Table 1 we combine the numbers for men and women to obtain combined SMRs which we interpret as RR for the respective cancer deaths.

As incidence data we take the respective cancer mortality rates for France, listed in column three of Table 1b). As exposure data we take the concentrations of As in the water supply of the affected population, 568 μg_{As}/L from 1955 to 1969 (Table 1 of Smith et al), whereas the average concentration of non-contaminated areas was 14 μg_{As}/L. With a water consumption of 600 L/yr that implies an intake of 332 mg_{As}/yr from water above the levels in non-contaminated areas (the latter being the reference for the SMRs). The resulting ERF slopes are shown in column four and the cancer deaths and damage costs per kg of emitted As in columns five and six, the latter calculated with Eq.6 of Part 1.

Table 1. Data and calculations for bladder, skin, kidney and lung cancer due to As. a) the data of Tables 2 and 3 of Smith et al [1998], with 95% CI in brackets.

	Observed deaths	Expected deaths	SMR, men	Observed deaths	Expected deaths	SMR, women
bladder	93	15.5	6.0 *[4.8,7.4]*	64	7.8	8.2 *[6.3,10.5]*
Kidney	39	25	1.6 *[1.1,2.1]*	34	12.4	2.7 *[1.9,3.8]*
liver	48	42	1.1 *[0.8,1.5]*	37	34.8	1.1 *[0.8,1.5]*
lung	544	143.2	3.8 *[3.5,4.1]*	154	49	3.1 *[2.7,3.7]*
skin	20	2.6	7.7 *[4.7,11.9]*	7	2.2	3.2 *[1.3,6.6]*

b) The SMRs for men and women, implied by part a), together with cancer mortality data for France, as deaths/yr per average person. The ERF slope is based on an intake of 332 mg_{As}/yr from drinking water in Smith et al [1998]. The damage cost per kg in the last column is for water intake only, without discounting.

	SMR, men+women	Deaths/yr, France	s_{ERF} [(deaths/yr)/(mg_{As}/yr)]	Deaths/kg_{As}, water only	€/kg_{As}
Bladder	6.7	0.000076	1.31E-06	0.000041	122.4
Kidney	2.0	0.000050	1.43E-07	0.000004	13.4
Lung	3.6	0.000494	3.91E-06	0.000122	364.9
Skin	5.6	0.000027	3.76E-07	0.000012	35.1

c) Non-fatal cancers, based on fatal cancers and survival rates. These numbers are for water intake only, without threshold and without discounting.

	Deaths/kg_{As}, water only	Survival rates	Non-fatal cancers/kg_{As}	€/kg_{As}
Bladder	0.000041	0.60	0.000061	9.8
Kidney	0.000004	0.65	0.000008	1.3
Lung	0.000122	0.15	0.000021	3.4
Skin	0.000012	0.90	0.000105	16.8

Adding up the damage costs for lung, bladder, kidney, and skin in Table 1b), the total comes to 347.1 €/kg_{As} from drinking water. Multiplying by the factor 3.3 of Eq.1 to account for the total inorganic As and by the unit cost of 3 million $€_{2010}$, we obtain a total cost of cancer deaths of 1,787 $€_{2010}/kg_{As}$, without discounting or threshold. The calculation for non-fatal cancers is shown in part c) of Table 3, based on survival rates in France [2], UK [3], and US [4]. We obtain the non-fatal cancers by multiplying the cancer deaths by survival rate/(1 - survival rate). After multiplying likewise by the factor 3.3 of Eq.1 and a unit cost of 159,767 $€_{2010}$, we find the cost of non-fatal cancers to be 105 $€_{2010}/kg_{As}$, without discounting or threshold.

1.4. Respiratory Symptoms and Chronic Bronchitis

Several recent studies have observed significant respiratory impacts of As [Parvez et al 2010 and Milton and Rahman 2002]. In addition significant lung function impairment has been found by von Ehrenstein et al [2005], Dauphiné et al [2010], Nafees et al [2011] and Chattopadhyay et al [2010]. Milton and Rahman report a significant increase of chronic bronchitis (CB) due to As in drinking water, but since their study population of 169 persons is much smaller than the 11,746 persons of Parvez et al [2010], we use the latter. Parvez et al carried out a prospective study of respiratory symptoms associated with chronic arsenic exposure in Bangladesh, with follow-up during four years. They find significant associations with respiratory symptoms, defined as chronic cough, breathing problem or blood in the sputum. From their data we extract the following relation between risk of respiratory symptoms and As concentration in the water supply

$$\Delta RR/\Delta conc = 0.0024/(\mu g_{As}/L) \quad . \qquad (5)$$

Since these symptoms are quite severe, comparable to what has been used in studies of chronic bronchitis, we assume that this relation can be combined with the incidence rates and monetary valuation that have been used by ExternE [2008] for chronic bronchitis. Multiplying Eq.5 by the background incidence rate of 0.00378 cases/yr in the EU and dividing by 0.6 $(mg_{As}/yr)/(\mu g_{As}/L)$ for the relation between As intake and concentration in the water supply we obtain the ERF slope as

$$s_{ERF} = 1.52E\text{-}5\ (cases/yr)/(mg_{As}/yr) \quad \text{for chronic bronchitis.} \qquad (6)$$

[2] http://fr.wikipedia.org/wiki/Cancer#Taux_de_survie_et_surmortalit.C3.A9 accessed 22 March 2015
[3] http://www.cancerresearchuk.org/cancer-info/cancerstats/survival/common-cancers/ accessed 22 March 2015
[4] http://seer.cancer.gov/statfacts/html/urinb.html accessed 22 March 2015

Multiplying s_{ERF} by the IF for water intake, by the cost of a case of CB, 210,000 $€_{2010}$ as per Table 2 of Part 1 and by the factor 3.3 of Eq.1, we obtain an undiscounted damage cost of 332 $€_{2010}/kg_{As}$ due to chronic bronchitis, without discounting or threshold.

Lung function impairment is difficult to value in monetary terms. A small loss is unlikely to be perceived as serious handicap by most people, if it is noticed at all. Nonetheless, it entails serious long term effects for the health of the body, effects that are visible in correlations between lung function and life expectancy. For example, Neas and Schwartz [1998] have found that a 10% decrement in predicted FEV1 (forced expiratory volume in 1 sec) increases the RR for mortality by a factor of 1.15 (CI 1.10-1.19). Combining the ERF for loss of lung function with the RR for LE loss per lung function loss, one obtains an estimate for part of the mortality impact. Extracting ERFs for reduction of FEV1 from the papers of von Ehrenstein et al, Dauphiné et al and Nafees et al (it is difficult to interpret the results of Chattopadhyay et al as an ERF for FEV1) and combining them with LE loss of Neas and Schwartz, we find that the result explains about 10 to 30% of the non-cancer mortality (details not shown here). Of course, a result of combining ERFs in such a manner is doubly uncertain, but in any case it strengthens the argument for the causality of these As impacts.

1.5. Neurotoxic effects

Strong evidence for neurotoxic effects of As has been found by Wasserman et al [2004 and 2007], von Ehrenstein et al [2007], O'Bryant et al [2011], and Kang et al [2007]. But for a quantitative interpretation there are some problems. Some of these studies do not control for possible confounding by other neurotoxic metals Hg, Pb and Mn. Such studies focus on infants and young children because their brains are most vulnerable to damage, and one has to use specialized tests, adapted to the respective regions and cultures, rather than standard IQ tests of the USA. A variety of different tests are used by different studies and it is not clear how the results relate to the IQ that is routinely measured in the USA. Here we use the studies of Wasserman et al because they are specifically for As in the water supply (in Bangladesh).

We use the relative reduction observed in these specialized tests as proxy for IQ loss. That is, of course, problematic because different test measure different functions of the brain and a loss due to As can affect different functions differently, but we do not know what alternative would be better. Taking the average of the IQ ("full scale") results of Wasserman et al [2004 and 2007] with this interpretation, we obtain the IQ loss of the study population

$$\text{IQ loss/concentration} = 0.027 \text{ IQ points}/(\mu g_{As}/L) \; . \qquad (7)$$

To obtain the ERF slope as loss rate per year, we multiply by the birth rate for which we take the current rate of the EU27, 0.0104 births/yr per person, and after division by 0.6 $(mg_{As}/yr)/(\mu g_{As}/L)$ we find

$$s_{ERF} = 0.00048 \text{ (IQ points/yr)}/(mg_{As}/yr) \quad \text{for neurotoxic impacts.} \qquad (8)$$

Multiplying further by the intake fraction, by the unit cost of 14,500 $€_{2010}$/IQpoint, and by the factor 3.3 of Eq.1 for total inorganic intake, we obtain the cost of neurotoxic impacts as 715 $€_{2010}/kg_{As}$.

1.6. Infant Mortality

Hopenhayn-Rich et al [2000] found significant associations between arsenic exposure and late fetal mortality, (RR = 1.7 [CI 1.5-1.9]), neonatal mortality (RR = 1.53 [CI 1.4-1.7]), and postneonatal mortality (RR = 1.26 [CI 1.2-1.3]), all for a concentration difference of 860 - 110 μg/L between the high and the low As exposure periods. They caution that the existing literature falls short of establishing a clear causal association between environmental arsenic exposure and reproductive health effects. However, further studies since then [Hopenhayn et al 2003, and Xu et al 2011] have found reduced birth weight after As exposure, which adds plausibility.

Combining the RR Hopenhayn-Rich et al [2000] with the birth rate of the EU 27 and the mortality rates in France for respective types of infant mortality, we find the results in Table 2, with the valuation of 2 * VPF per infant death.

Table 2. RR of Hopenhayn-Rich et al [2000] for infant mortality, and calculations (with 6,000,000 €$_{2010}$/infant death).

	late fetal mortality,	neonatal mortality	postneonatal mortality
RR	1.7 [CI 1.5-1.9]	1.53 [CI 1.4-1.7]	1.26 [CI 1.2-1.3]
$\Delta RR/(\mu g_{As}/L)$	0.00093	0.00071	0.00035
Birth rate, births/(person.yr)	0.0104	0.0104	0.0104
deaths per birth	0.004	0.002	0.001
s_{ERF}, (deaths/yr)/(mg_{As}/yr)	6.47E-08	2.45E-08	6.01E-09
€/kg_{As}	17.8	4.6	1.1

The total comes to 9.3 €/kg_{As} due to water intake. Multiplying by the ratio 3.3 for total intake/intake from water we obtain the total cost of infant mortality as 59 €$_{2010}$/kg_{As}, without discounting or threshold.

This amounts to about 2% of the non-cancer mortality cost. That infant mortality contributes little to the total damage cost is a result we have also found for mortality due to $PM_{2.5}$ [Rabl 2003]. The explanation is, very roughly, that infant mortality is small compared to adult mortality: most of people die as adults, not as infants.

1.7. Diabetes

Rahman et al [1998] find that As is a risk factor for diabetes, but until recently the evidence did not appear sufficiently strong. For instance, the review by Navas-Acien et al [2006] concluded that the available evidence was inadequate to establish a causal role of arsenic in diabetes. However, more recently a number of studies have found significant associations and we believe that the evidence is sufficient for the calculation of the associated damage cost.

Navas-Acien et al [2008] carried out a cross-sectional analysis of the NAHNES data for 2003-2004 and found a significant association. Whereas Steinmaus et al [2009] in an analysis of the same data found no evidence of increased diabetes risk with arsenic exposure, a re-analysis by Navas-Acien et al [2009a], with more recent and more complete NAHNES data for 2003-2006, reconfirmed a significant effect. Likewise significant associations have been found by

Kim et al [2013] in a case-cohort study of American Indians in Arizona; James et al [2013] in a case-cohort study of a population in South-Central Colorado; Jovanovic et al [2012] in a cross-sectional study of the Middle Banat region of Serbia; and Del Razo et al [2011] in a cross-sectional study of Zimapán and Lagunera in Mexico.

The results of Navas-Acien et al, Steinmaus et al and of Kim et al are difficult to use for quantification of impacts because they are based on urinary As, for which we have no reliable link to As exposure. By contrast, James et al [2013], and Jovanovic et al [2012] also provide data on the As concentration in the water supply. The RR and the corresponding exposure intervals are shown in Table 3.

Table 3. RR and exposure intervals for diabetes.

Study	RR (CI)	$\mu g_{As}/L_{water}$	$\Delta RR/(\mu g_{As}/L)$
Jovanovic et al [2012]	1.43 (0.99-2.07)	32	0.013
James et al [2013]	1.27 (1.01-1.59)	15	0.018
Mean			0.0157

To obtain the ERF the ΔRR has to be multiplied by the diabetes incidence rate. Whereas prevalence data are available for most countries, incidence data are hard to find, except for the USA where the incidence rate in 2010 was 8.1 per yr per 1000 and the prevalence was 6.5% [http://www.cdc.gov/diabetes/statistics/incidence/fig2.htm]. We use the incidence/prevalence ratio of the USA

incidence/prevalence 8.1/65 = 0.12 per year

for other countries as well, in particular for France and much of Europe where the prevalence is 4%. Thus we take the incidence rate of diabetes in France to be

diabetes incidence rate in France = 0.04 * 0.12 = 0.0048 per yr.

Multiplying $\Delta RR/\Delta conc = 0.0157$ ($\mu g_{As}/L$) by the incidence rate and dividing by the dose conversion factor 0.6 (mg_{As}/yr)/($\mu g_{As}/L$), we obtain the ERF slope as

$$s_{ERF} = 0.0048 * 0.0157/0.6 = 0.000126 \text{ (cases/yr)/(mg}_{As}\text{/yr) water intake .} \quad (9)$$

For the cost of diabetes we cite the DALY scores of Huijbregts et al [2005] who value an average case of diabetes as 2.2 DALY. Multiplying Eq.9 by 2.2 DALY/case of diabetes, by the cost of 84,000 $€_{2010}$/DALY and by the IF due to water intake, 31.1 mg_{As}/kg_{As} we obtain the cost of diabetes as

[0.000126 (cases/yr)/(mg_{As}/yr)] * 31.1 mg_{As}/kg_{As} * 2.2 * 84,000 €/case = 723 €/kg_{As}.

With the assumption that all ingestion of inorganic As is equally toxic we further multiply this by the ratio 3.3 of Eq.1 to find that the undiscounted contribution of diabetes to the damage cost of As is 2,411 $€_{2010}/kg_{As}$ without discounting or threshold.

1.8. Thresholds and Summary for As

As threshold we take the maximum daily intake by ingestion, 0.3 $\mu g_{As}/kg_{body}$/day, of EPA. We apply the threshold even to cancers, because As only promotes but does not initiate the development of cancers. We relate the maximum daily intake to the corresponding urinary As concentration by using the biokinetic model of Calderon et al [1999] which implies that this intake corresponds to a urinary concentration of 11.8 $\mu g_{As}/g_{creat}$. We fit the exposure

distribution of InVS [2011] with μ_g = 11.96 $\mu g_{As}/g_{creat}$ and σ_g = 2.4, and find that the fraction of the incremental exposure above the threshold is f_{thr} = 0.80, calculated according to Eq.14 of Part 1. The results are summarized in Table 4. Mortality contributes 50% of the total discounted damage cost.

Table 4. Summary of damage costs contributions for As, in €$_{2010}$/kg$_{As}$, assuming all inorganic As to be equally toxic. The population fraction above threshold is f_{thr} = 0.80, applied to all endpoints. Cases are without f_{thr}, with units YOLL for non-cancer mortality and IQ points for IQ loss.

Endpoint	Cases/kg$_{As}$	Undiscounted, no threshold	Lag [yr]	Discount factor	Discounted, no threshold	Discounted, with threshold
Non-cancer mortality	9.95E-03	2,606	10	0.68	1,760	1,413
Cancer deaths	5.96E-04	1,787	20	0.46	816	655
Non-fatal cancers	6.54E-04	105	20	0.46	48	38
Chronic bronchitis	1.58E-03	332	10	0.68	224	180
IQ loss	4.93E-02	715	0	1.00	715	574
Infant deaths	9.88E-06	59	10	0.68	40	32
Diabetes	1.30E-02	2,411	10	0.68	1,629	1,308
Total cost, €$_{2010}$/kg$_{As}$		8,014			**5,231**	**4,200**

2. Cadmium

2.1. General Considerations

The most important impacts of Cd are kidney disease, osteoporosis, cancer, cardiovascular disease and premature mortality [WHO 1992, ATSDR 2012]. Human exposures to cadmium result primarily from industrial activities (fossil fuel combustion, metals production, cement production, and waste incineration), from phosphate fertilizers, and from natural sources. Average daily intake from food in most countries is in the range of 3.6 to 9.1 mg$_{Cd}$/yr. Tobacco smoke is a major source, because the fraction absorbed from inhalation is about four times as high as the fraction absorbed from ingestion. Compared to non-smokers cigarette smokers typically have about twice as much Cd in their kidneys.

For typical chronic exposures of the general population the urine cadmium level increases in proportion to the amount of cadmium stored in the body. Cd is stored in mostly in the kidneys and bones, with a half-life of several decades. The most commonly used biomarker for Cd exposure is urinary excretion measured in units of $\mu g_{Cd}/g_{creat}$ per g of creatinine in urine. Some studies have also used cadmium levels in the blood. Whereas cadmium levels in the blood mainly reflect the exposure during recent weeks or months, urinary Cd reflects chronic exposure during the preceding decades, urinary Cd concentration reaching a peak around age 50. Because of interaction with iron in the body, there are large sex differences in the metabolism of Cd. In the NHANES data set of almost 14000 individuals the geometric mean creatinine-corrected urinary cadmium level was 0.28 $\mu g_{Cd}/g_{creat}$ in men and 0.40 $\mu g_{Cd}/g_{creat}$ in women [Menke et al 2009].

Quite a few studies provide information for the relation between Cd intake and the resulting levels of the biomarkers. The data of Jarup et al [1998] concern industrial workers and we

disregard them because industrial exposure involves mainly inhalation of Cd, rather than ingestion. The studies of Olsson et al [2002], Julin et al [2011], Sirot et al [2008] and He et al [2013] are based on detailed dietary intake data for relatively small groups of individuals, in the range of about 50 to a few hundred. Because of large individual variability and regional differences in diet and Cd pollution it is not surprising that these studies report fairly different results for the relation between intake and the biomarker levels. For the USA representative data can be found in ATSDR [2012] for intake and blood Cd and in Menke et al [2009] for urinary Cd.

In Table 5 we show data for the relation between Cd intake and biomarkers, for nonsmokers in Sweden and for average populations in the USA. The ratios happen to be very similar, the ones for Sweden being somewhat lower which could be due to the fact that smokers get a significant non-dietary Cd dose. In this paper we use the ratios for the USA because they are representative of a large population.

Table 5. Data for the relation between Cd intake and biomarkers.
The numbers for Sweden are for non-smokers, from Olsson et al [2002], the ones for USA are for the average population, from ATSDR [2012] for intake and blood-Cd and Menke et al [2009] for Urinary-Cd (U-CD).

	Intake	U-Cd	U-Cd/intake	Blood-Cd	Blood-Cd/intake
	mg_{Cd}/yr	$\mu g_{Cd}/g_{creat}$	$(\mu g_{Cd}/g_{creat})/(mg_{Cd}/yr)$	$\mu g_{Cd}/L$	$(\mu g_{Cd}/L)/(mg/yr)$
Men, Sweden	7.10	0.18	0.025	0.21	0.030
Women, Sweden	5.43	0.30	0.055	0.29	0.054
Men, USA	9.59	0.28	0.029	0.30	0.031
Women, USA	7.12	0.40	0.056	0.33	0.046
Men&women, average, USA			0.043		0.039

2.2. Mortality

Associations of mortality with Cd exposure have been reported by several epidemiological studies [Matsuda et al 2003; Nishijo et al 2004; Nakagawa et al 2006; Nawrot et al 2008; Menke et al 2009; Tellez-Plaza et al 2012]. Some of these do not provide enough information for quantification. For instance Nishijo et al used urinary beta-2-microglobulin as indicator of exposure for which we do not know the relation to intake.

Nawrot et al [2008] compared all-cause mortality for the same study populations as Nawrot et al [2006] did for cancers. A population of randomly selected 956 individuals in Belgium (approximately half from a low exposure and half from a high exposure area) was studied with follow-up from 1985 to 2007. They find that RR for all-cause mortality increases by a factor of 1.20 for a doubling of urinary Cd which estimate as in exposure increase of 0.54 U-$\mu g_{Cd}/g_{creat}$. That implies a risk increase per urinary Cd of

$$\Delta RR/\Delta exposure = 0.37/(U\text{-}\mu g_{Cd}/g_{creat}).$$

Tellez-Plaza et al followed 8,989 participants of the NHANES 1999-2004 survey for an average of 4.8 yr, using both urinary and blood Cd concentrations. The exposure ranges are specified as 80^{th} and 20^{th} percentiles of the Cd distributions. For urinary Cd concentrations they find an all-cause mortality RR of 1.52 (CI 1.00-2.10) corresponding to an exposure range

from 0.14 U-$\mu g_{Cd}/g_{creat}$ (20^{th} percentile) to 0.57 U-$\mu g_{Cd}/g_{creat}$ (80^{th} percentile). That implies a risk increase per urinary Cd of

$$\Delta RR/\Delta exposure = 1.21/(U\text{-}\mu g_{Cd}/g_{creat}), \quad (13)$$

about 3.3 times larger than the analogous result of Nawrot et al [2008]. Here we use Tellez-Plaza et al 2012 because it covers a wider exposure range than Menke et al and the exposure range is measured with much greater precision than for Nawrot et al (who indicate the exposure range only as ratio, the absolute magnitude being less clear). Multiplying Eq.13 by the LE loss per ΔRR of Eq.2 of Part 1 and by the ratio 0.043 $(\mu g_{Cd}/g_{creat})/(mg_{Cd}/yr)$ of Table 5, we obtain the ERF slope as

$$s_{ERF} = 7.62E\text{-}03\ (YOLL/yr)/(mg_{Cd}/yr) \text{ for all-cause mortality, with Eq.13.} \quad (14)$$

Further multiplication by the IF of 260.1 mg/kg (Table 1 of Part 1) and by VOLY (Table 2 of Part 1) yields the corresponding undiscounted cost as 166,438 $€_{2010}/kg_{Cd}$.

For blood Cd concentrations Tellez-Plaza et al find an all-cause mortality RR of 1.50 (CI 1.07-2.83) corresponding to an exposure range from 0.22 $\mu g_{Cd}/L_{blood}$ (20^{th} percentile) to 0.80 $\mu g_{Cd}/L_{blood}$. That implies a risk increase per blood Cd of

$$\Delta RR/\Delta exposure = 0.86/(\mu g_{Cd}/L_{blood}). \quad (15)$$

Multiplying this equation by the LE loss per ΔRR and by the ratio 0.039 $(\mu g_{Cd}/L)/(mg_{Cd}/yr)$ of Table 5, we obtain the ERF slope as

$$s_{ERF} = 4.94E\text{-}03\ (YOLL/yr)/(mg_{Cd}/yr) \text{ for all-cause mortality, with Eq.15.} \quad (16)$$

The corresponding cost is 107,937 $€_{2010}/kg_{Cd}$. Averaging the numbers for urinary and for blood Cd, we obtain 137,187 $€_{2010}/kg_{Cd}$ for the undiscounted cost due to all-cause mortality.

2.3. Cancers

Cd has been recognized as carcinogen by EPA and by the International Agency for Research on Cancer [IARC 1993]. Joseph [2009] in a review of mechanisms of cadmium carcinogenesis concludes that the link between Cd exposure and lung cancer is causal. The IRIS web site of EPA shows an ERF for lung cancers due to inhalation, as

Air Unit Risk = 1.8E-03 lung cancers per $(\mu g_{Cd}/m^3)$ per 70 yr.

This implies a damage costs of 40 $€/kg_{Cd}$ from lung cancers due to inhalation of Cd. However, this unit risk estimate has not been revised since 1992, and like all unit risk factors of EPA, it is the upper bound of the 95% CI. In calculating this cost of 40 $€/kg_{Cd}$ we have for simplicity assumed that all lung cancers are fatal, even though the fatality rate is about 85% for lung cancers. In any case, the following epidemiological studies indicate that Cd causes far more cancers than implied by this unit risk, probably because total intake is very much larger than inhalation.

In the following epidemiological studies we assume that the observed RR, even when it was observed for fatal plus non-fatal cancers of a given type can be used equally for fatal cancers of that type. Since the earlier worker-based studies several epidemiological studies have

assessed the cancer risk of the general population. Nawrot et al [2006] have compared cancer incidence and mortality (both total cancers and lung cancers) between two populations in Belgium, one at a site with high Cd pollution from the metals industry, the other a reference site. The total sample size was 994, with median follow-up period of 17.2 yr. They found that a doubling of urinary Cd excretion was associated with an RR of 1.31 (1.03–1.65) for all cancers and 1.70 (1.13–2.57) for lung cancers. After excluding 42 individuals who had been exposed as workers and correcting for As exposure (with two models, called A and B [5]), the relative risks were only very slightly lower: 1.26 (0.97–1.64) for all cancers, and 1.61 (1.00–2.59) (model A) and 1.57 (0.96–2.56) (model B) for lung cancer. We believe that even these latter RR values are sufficiently close to significance according to the usual criterion, and so we use them to estimate the cancers due to Cd.

Nawrot et al indicate the corresponding urinary Cd range only as ratio of two, rather than in absolute terms as needed for damage cost calculations. We estimate the range by assuming that its midpoint is the mean of the urinary Cd levels in the low and in the high exposure areas, namely (0.63 + 0.99)/2 = 0.81 U-$\mu g_{Cd}/g_{creat}$. Since the lower limit of a two-fold range is at 2/3 of its midpoint, the lower limit of the range, and hence its width, is 2*0.81/3 = 0.54 U-$\mu g_{Cd}/g_{creat}$. Thus we obtain

$$\Delta RR/\Delta exposure = 0.59/(0.54\ U\text{-}\mu g_{Cd}/g_{creat}) \text{ for lung cancers} \qquad (10)$$

for lung cancer, taking the average RR for models A and B. The lung cancer mortality rate in France is 0.00049 deaths/yr.person [INSERM 2009]. Multiplying Eq.10 by this mortality rate and by the ratio 0.043 ($\mu g_{Cd}/g_{creat}$)/(mg_{Cd}/yr) of Table 5, we obtain the ERF slope as

$$s_{ERF} = 2.29E\text{-}05 \text{ (deaths/yr)/}(mg_{Cd}/yr) \text{ for lung cancers.} \qquad (11)$$

Multiplying this ERF slope by the IF = 260.1 mg/kg and by the unit cost of cancer deaths we obtain the undiscounted cost contribution of lung cancers as 17,897 $€_{2010}/kg_{Cd}$.

For all cancers Nawrot et al [2006] find a risk increase of ΔRR/Δexposure = 0.26/(0.54 U-$\mu g_{Cd}/g_{creat}$), and a fraction 50/70 of these cancers is fatal. With the total cancer mortality rate of 0.00255 deaths/yr.person [INSERM 2009], we find an ERF slope of 5.22E-05 (deaths/yr)/(mg_{Cd}/yr) which multiplied by the IF = 260.1 mg/kg yields 0.0136 cancer deaths/kg_{Cd}. The corresponding cost is 29,102 €/kg_{Cd}, without threshold and discounting.

Significant associations of Cd exposure have also been reported for breast cancer by [McElroy et al 2006] and by Gallagher et al [2010], with very similar results. Cd has several properties, including binding to and stimulation of the estrogen receptor alpha and inhibition of DNA repair, which are potential risk factors for breast cancer carcinogenesis. McElroy et al carried out a population-based case–control study (246 women, aged 20 – 69 years, with breast cancer and 254 age-matched control subjects); relative to the lowest quartile (<0.26 $\mu g_{Cd}/g_{creat}$) women in the highest quartile (> 0.58 $\mu g_{Cd}/g_{creat}$) had an odds ratio = 2.29 (1.3 to 4.2). Gallagher et al carried out a case-control study with two populations, one in Long Island,

[5] Model A = with data calculated from geometric mean urinary excretion of arsenic within every district for 260 people with missing data for 24-h urinary arsenic excretion.
Model B = with data calculated from multiple regression equation that included the predictor variables sex, age, linear and squared terms of age, smoking, and nine design variables coding for the ten districts for 260 people with missing data for 24-h urinary arsenic excretion.

NY, (100 with breast cancer and 98 without), the other one a representative sample of US women (NHANES 1999-2008, 92 with breast cancer and 2,884 without); compared to the lowest quartile (<0.22 $\mu g_{Cd}/g_{creat}$), the odds ratio in the highest quartile (> 0.60 $\mu g_{Cd}/g_{creat}$) was 2.69 (1.07, 6.78) for LI women and 2.22 (0.89, 5.52) for US women. Unfortunately these authors report only interquartile ranges for the urinary Cd concentrations, rather than the actual means in each group. We estimate the exposure range from the fact that exposures are approximately lognormal and that the parameters of the lognormal distributions can be estimated by fitting the interquartile ranges. For McElroy et al we fit with geometric mean 0.395 and geometric standard deviation 1.8 and obtain a range from 0.17 to 0.86 $\mu g_{Cd}/g_{creat}$, and for Gallagher et al we fit with geometric mean 0.37 and geometric standard deviation 2.1 and obtain a range from 0.15 to 0.98 $\mu g_{Cd}/g_{creat}$. We also take the odds ratio as an approximation of the RR. Averaging over the ΔRR/Δexposure values implied by these assumptions for each of the three populations, we thus obtain

$$\Delta RR/\Delta exposure = 1.79/(U-\mu g_{Cd}/g_{creat}) \text{ for breast cancer deaths.} \quad (12)$$

The breast cancer mortality rate in France is 0.000189 deaths/yr.person [INSERM 2009]. Multiplying Eq.12 by this mortality rate, by the ratio 0.056 $(\mu g_{Cd}/g_{creat})/(mg_{Cd}/yr)$ for women of Table 5, by the IF of Table 1 of Part 1, and by the unit cost of fatal cancers Table 2 of Part 1, we obtain the damage cost contribution as 14,835 €/kg_{Cd} from breast cancers. That is consistent with our results for Nawrot et al [2006] since the sum of lung cancers (17,897 €/kg_{Cd}) and breast cancers is less than the total cost of cancers (29,102 €/kg_{Cd}).

As for other cancers, associations with prostate cancer [Verougstraete et al 2003; Vinceti et al 2007], pancreatic cancer [Schwartz and Reis 2000] and kidney cancer [Il'yasova and Schwartz 2005] have been studied but the evidence is not sufficiently clear.

The lung cancer result implied by Nawrot et al [2006] is more than two orders of magnitude above the result implied by the EPA unit risk for lung cancers due to inhalation. However, being based on studies of workers in the metals industry, the EPA unit risk accounts only for inhalation. We do not find this difference in cancers surprising in view of the large ratio of the ingestion and inhalation IFs, the healthy worker effect, and the fact that studies based on urinary Cd account for chronic exposures and long lag times.

In any case we do not count the costs from cancer deaths for the totals because they are already implicitly included in the mortality costs of Section 2.2. The only cancer costs that we will count for the total damage cost of Cd are non-fatal cancers. For that purpose we note that Nawrot [2006] indicates that of the 70 cancers observed in his study population 50 were fatal. Thus we multiply the above cancer deaths, 0.0136 cancer deaths/kg_{Cd}, by 20/50 to obtain 0.0053 non-fatal cancers/kg_{Cd}, With the corresponding unit cost of Table 2 of Part 1, the damage cost of non-fatal cancers is 868 $€_{2010}$/kg_{Cd}, without threshold and discounting.

2.4. Osteoporosis

Numerous studies provide clear evidence of associations between Cd exposure and osteoporosis, see e.g. Gallagher et al [2008] and the reviews by Jarup et al [1998] and Nawrot et al [2010]. However, these studies are not sufficient to derive an estimate of damage costs because osteoporosis does not incur a cost until there is a fracture. We have found only one study that measures a relation between Cd exposure and fracture risk [Engström et al 2011].

Comparing non-smoking women with U-Cd < 0.50 $\mu g/g_{creat}$ and those with U-Cd ≥ 0.75 $\mu g/g_{creat}$ these authors find that among never-smokers, the ORs (95% CIs) were 2.03 (1.33-3.09) for any first fracture, 2.06 (1.28-3.32) for first osteoporotic fracture, 2.18 (1.20-3.94) for first distal forearm fracture, and 1.89 (1.25-2.85) for multiple incident fractures. Let us take the RR of 2.06 for first osteoporotic fracture risk. Since the average concentrations of the groups are not provided, we estimate the exposure range to be roughly 1.0 – 0.25 $\mu g/g_{creat}$ = 0.75 $\mu g/g_{creat}$. Even though this study involves only women, several studies of osteoporosis have found essentially the same relation between Cd and osteoporosis for men and for women [e.g. Alfven et al 2000; Wu et al 2010]. Therefore we assume that the fracture risk of Engström et al is also the same for men and for women

$$\Delta RR/\Delta exposure = 2.06/(0.75\ U\text{-}\mu g_{Cd}/g_{creat}) \text{ for risk of fracture.} \quad (17)$$

A frequent type of fracture is a hip fracture (more precisely fracture of the neck of the femur), and in terms of treatment cost and suffering it is the most serious. Frequently such fractures entail severe long term consequences for the quality of life [6]. This is reflected in the DALY scores of Salomon et al [2012]:

Fracture of neck of femur: short term, with or without treatment 0.308,
Fracture of neck of femur: long term, with treatment 0.072,

The average age for suffering a hip fracture is 77 years old for women and 72 years old for men [Baumgaertner and Higgins 2002]. Since the average remaining LE after age 75 is 13 yr, we take the total DALY score of a hip fracture as 0.308 + (13 – 1) * 0.072 = 1.17 DALY. For the costs in France we cite numbers of Mutuelle Saint Martin [7] which imply an average treatment cost of 19,000 $€_{2010}$/fracture. With the cost of suffering the total cost of a hip fracture comes to 19,000 + 1.17*84,000 = 117,448 $€_{2010}$/fracture.

Their incidence in France is 67,000 per yr in a total population of 65 million [Maravic et al 2011], implying an incidence rate of 0.00103 per person per year. Multiplying Eq.17 by the ratio 0.043 $(\mu g_{Cd}/g_{creat})/(mg_{Cd}/yr)$ of Table 5 and by the incidence rate, we find an ERF slope of

$$s_{ERF} = 6.22E\text{-}05 \ \ (\text{fractures/person/yr})/(mg_{Cd}/yr). \quad (18)$$

Further multiplication by the IF of 260.1 mg/kg and the cost per fracture yields the undiscounted cost per kg of emitted Cd as 1,899 $€_{2010}/kg_{Cd}$, without discounting and threshold.

2.5. Other end points

There are additional end points that have been associated with Cd exposure in epidemiological studies. In particular we cite studies of large samples of the general populations. Peters et al [2010] find significant associations with stroke and heart failure in a sample of about 12000 participants in the 1999-2006 National Health and Nutrition Examination Survey (NHANES). Lee et al [2010] find associations with cardiovascular disease in a sample of 1908 adults in Korea. Everett and Frithsen [2008] find associations with myocardial infarction in 4912 participants of the National Health and Nutrition

[6] See e.g. http://en.wikipedia.org/wiki/Hip_fracture
[7] http://www.saintmartin.com.fr/la-fracture-du-col-du-femur/

Examination Survey III (1988-1994). These studies would be difficult to quantify in monetary terms, but they provide added plausibility for the reality of the mortality impacts.

Kidney disease is another important endpoint of Cd. In particular Ferraro et al [2010 and 2011] find significant associations in the National Health and Nutrition Examination Survey III; unfortunately they only state their odds ratios for two groups, above and below 1 $\mu g_{Cd}/g_{creat}$, without any information on the corresponding exposure range, so it is not possible to quantify the impacts. Another large NHANES based study [Navas-Acien et al 2009b] also finds very significant renal impacts; however, their endpoints, albuminuria and the estimated glomerular filtration rate, are merely general indicators of kidney problems and not sufficiently specific as measure of kidney disease to allow monetary valuation.

2.6. Thresholds and Summary for Cd

In Table 6 we present a summary of our damage cost calculations. Since the RR of Tellez-Plaza [2012] are for all-cause mortality, without any information about the contribution of cancers, we do not add the cancer deaths of Section 3.2, taking them merely as an indication of the plausibility of the 137,187 €/kg_{Cd} for all-cause mortality, before discounting. But we do add fractures as an independent cost contribution.

As threshold we take the Minimal Risk Level for chronic ingestion dose according to ATSDR [2012], namely a maximum daily intake of 0.1 ($\mu g_{Cd}/kg_{body}$/day) which we convert to a urinary concentration of 0.109 $\mu g_{Cd}/g_{creat}$, using the conversion factor of 0.043 $(\mu g_{Cd}/g_{creat})/(mg_{Cd}/yr)$ of Table 5 together with a body weight of 70 kg. We fit the exposure distribution of InVS [2011] with $\mu_g = 0.29$ $\mu g_{Cd}/g_{creat}$ and $\sigma_g = 2.0$ and find that the fraction of the incremental exposure above the threshold is $f_{thr} = 0.98$, calculated according to Eq.14 of Part 1. Mortality contributes 98% of the total discounted damage cost.

Table 6. Summary of damage costs contributions for Cd, in $€_{2010}/kg_{Cd}$.
The population fractions above threshold are $f_{thr} = 0.98$, applied to all endpoints.
Unit for mortality cases is YOLL.

Endpoint	Cases/kg_{Cd}	Undiscounted, no threshold	Lag [yr]	Discount factor	Discounted, no threshold	Discounted, with threshold
Mortality	1.633	137,187	10	0.68	92,679	91,168
Non-fatal cancers	0.005	868	20	0.46	396	390
Fractures	0.016	1,899	10	0.68	1,283	1,262
Total $€_{2010}/kg_{Cd}$		**139,954**			**94,358**	**92,820**

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Abbreviations and symbols: see Part 1 of this series.

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