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Economic cost of fractures caused by dietary cadmium exposure

SWEDISH CHEMICALS AGENCY

Economic cost of fractures caused by dietary cadmium exposure

Foreword

The use of chemicals is of great benefit to human welfare, but several of them also have adverse effects on health and the environment. This applies to both intentional and unintentional use. Only a small number of studies have made an economic valuation of the adverse effects of chemicals on health. This study is an attempt to estimate the cost of fractures caused by dietary cadmium exposure.

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Swedish Chemicals Agency

Contents

Summary

This report is based on the results of two recently published medical reports and a European health economic study. The two medical reports show, among other things, a statistically significant association between cadmium exposure from food and the risk of fractures. This applies to both men and women. The health economic study shows that the economic valuation of the burden of fractures amounts to 39 billion SEK per year in Sweden.

Based on these studies we have calculated that the economic cost of fractures caused by cadmium in food amounts to approximately 4.2 billion SEK per year in Sweden. The costs are health care costs for these individuals in the short and long term and costs of lower quality of life and shortened life expectancy for those who suffer fractures, mostly the elderly.

An important conclusion is therefore that there are large social benefits to be gained by reducing cadmium intake through food and that increased intake of cadmium in food is likely to increase the economic costs of fractures. It is important to reduce the flow of cadmium to arable soil through the air and various forms of fertiliser use.

Sammanfattning

Denna rapport bygger på resultaten från två nyligen publicerade medicinska rapporter samt en europeisk hälsoekonomisk studie. De förstnämnda visar bland annat att det finns ett statistiskt säkerställt samband mellan kadmiumintag via maten samt risken för att drabbas av en fraktur. Detta gäller både män och kvinnor. Den hälsoekonomiska studien visar att de samhällsekonomiska kostnaderna för frakturer uppgår till 39 miljarder kronor per år i Sverige.

Utifrån dessa studier och genom egna beräkningar har vi kommit fram till att den *samhällsekonomiska kostnaden för frakturer orsakade av höga kadmiumhalter i maten, grovt sett, uppgår till 4,2 miljarder kronor per år*. Kostnaderna utgörs dels av vårdkostnader för dessa personer på kort och på lång sikt, dels av kostnader för lägre livskvalitet och förkortad livslängd för de, oftast äldre, människor som drabbas av frakturer.

En viktig slutsats är därför att det finns stora samhällsvinster att hämta genom att sänka kadmiumintaget via maten. Omvänt gäller att ökade kadmiumintag i maten riskerar att öka de samhällsekonomiska kostnaderna för benbrott.

1 Introduction

This report is aimed at describing in monetary terms the effects of people being exposed to cadmium through food, as a result of cadmium having been dispersed in the environment, and in particular on arable land. It is therefore possible to compare some of the costs resulting from cadmium in food with other costs in society.

Calculating the *economic costs* of environmental pollution in this way is relatively uncommon in the area of chemicals. On the other hand, it is a common method for example in the areas of transport policy and health economics. Economic cost estimates are made to compare different road projects or different medicines and methods of treatment with one another in order to make it easier to allocate priorities between various conceivable alternative projects or measures.

Dispersal of chemicals to nature and humans is something that takes place continuously throughout the world, but at the same time is a relatively invisible process leading to gradual changes that are difficult for most people to comprehend. There is therefore a risk of measures to arrest this change in the human environment being given low priority in comparison with measures in other area of society where the effects are clearer.

We hope to contribute to making it clear what great economic effects the dispersal of chemicals in nature actually has. We do so by combining results from medical and health-economic research.

2 Aim

Sweden is one of the countries in the world with the highest risk of sustaining fractures – particularly hip fractures[1]. Fractures lead to great suffering and high costs of medical and social care for society[2]. At the same time, two recently published studies show that there is an association between dietary exposure to cadmium and the risk of osteoporosis and fractures. Another study shows that the economic costs of fractures are very high in Sweden, over SEK 39 billion per year, and the costs are expected to rise in line with ageing of the population. An unknown share of these costs is due to high dietary cadmium intake. This report is therefore aimed at calculating how great the economic costs of fractures related to high cadmium levels in food are in Sweden.

In addition, the report tests the possibility of carrying out economic valuation studies in the area of chemicals.

3 Method

The method employed in writing this report has been to use and link together the research results from medical science and health-economic science. This report is principally based on other reports, namely:

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[1] Kanis et al, 2002.
[2] Ström et al, 2011.

- Reference Study A1. Engström A. (2011) *Cadmium As A Risk Factor For Osteoporosis And Fractures In Women,* Academic thesis at Karolinska Institutet, which is based on the following two published articles:

1) Engström A, Michaëlsson K, Suwazono Y, Wolk A, Vahter M, Åkesson A. (2011) Long-term cadmium exposure and the association with bone mineral density and fractures in a population-based study among women. *J Bone Miner Res*. 26:486-95; 2011.

2) Engström A, Michaëlsson K, Vahter M, Julin B, Wolk A, Åkesson A. (2012) Associations between dietary cadmium exposure and bone mineral density and risk of osteoporosis and fractures among women. *Bone*. 50:1372-8.

- Reference Study A2. Thomas, L DK, Michaëlsson K, Julin B, Wolk A and Åkesson A. *(2011)*Dietary Cadmium Exposure and fracture incidence Among Men: A population-Based Prospective Cohort Study*, J Bone Miner Res,* 7:1601-8, 2011.

- Referensstudie B. Ström O, Borgström F, Kanis J A, Compston J, Cooper C, McCloskey E V and Jönsson B (2011) Osteoporosis: burden, health care provision and opportunities in the EU*, Arch Osteoporos, 1-2:59-155, 2011*.

On the basis of Reference Studies A1 and A2, some of the authors at Karolinska Institutet have calculated what proportion of the studied fractures can be attributed to elevated dietary levels of cadmium.

Reference Study B gives us the aggregate economic cost of fractures. By multiplying the proportion of fractures due to increased cadmium intake by the total economic cost of fractures, the economic cost of fractures due to cadmium intake is obtained.

In addition to this, a broad review of the literature has been conducted.

3.1 Limitations and assumptions

Only economic costs of increased incidence of fractures are studied, not costs of any other health effects related to cadmium exposure.

Only economic costs linked to dietary cadmium exposure are included, not increased costs due to exposure to cadmium through smoking. The principal assumptions made for the calculations in this report are stated below. For the assumptions made in the reference reports, reference should be made to these reports. Other assumptions are described in the relevant section.

- The calculations of the economic costs of fractures relate to individuals aged 50 or over.

- The study does not correct differences in age groups investigated between the different studies referred to above. Reference Study B studies the economic costs for all individuals over the age of 50, while Study A1 only studies the risks of fracture for women aged 56 to 69 and Study A2 covers men aged 45 to 79. We therefore assume that the increase in fracture risk at higher cadmium intake is not affected by the somewhat varying age range.

- The calculations are based on the assumption that the distribution of different fractures is sufficiently similar in the different studies for it to be possible for the results to be combined.
- The calculations include individuals who are or have been smokers.

- The studies are based on individuals who have not previously had a fracture. This means that a large proportion of those who have a high fracture risk have been excluded from the studies, A1 and A2, which may affect the results.

4 Background

4.1 Osteoporosis and fractures in Sweden

In this study we will principally discuss how great an impact elevated cadmium intake has on the number of fractures. A brief and general introduction is therefore first given to the subject of osteoporosis and fractures.

4.1.1 High incidence of fractures in Sweden

The incidence of fractures is high in Sweden, Norway and Iceland compared with the rest of Europe[3], see Figure 1. The reason for the large geographical differences is not known, although several factors can be imagined to be significant. Some of the factors will be discussed later.

Figure 1. Ten-year risk of hip fracture among women in Sweden compared with other countries; the risk in Sweden is set at 1.
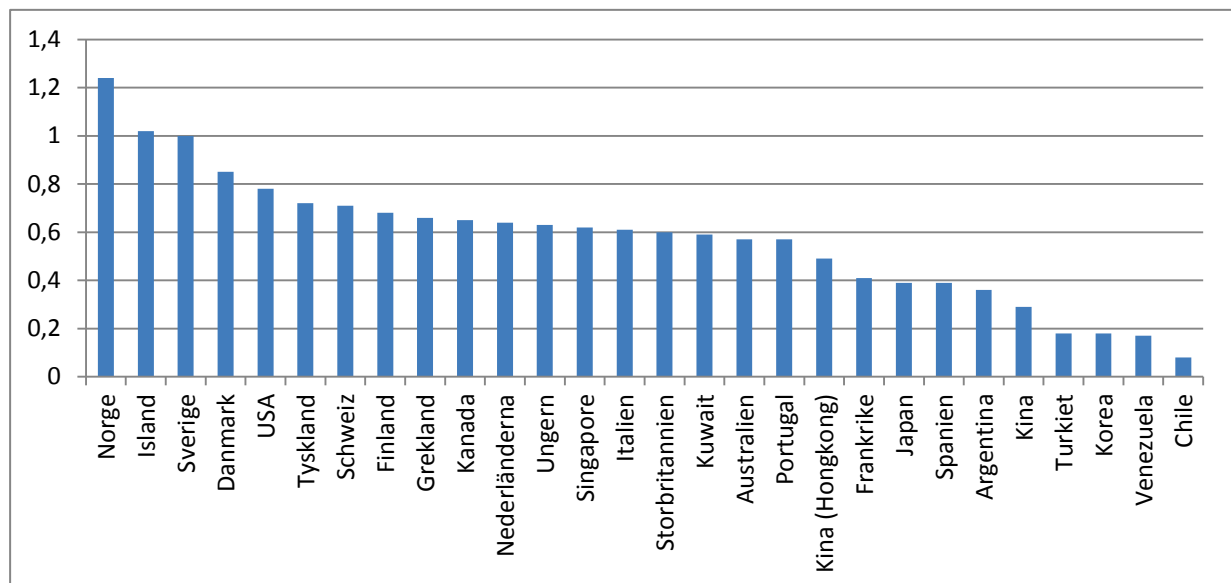
4.1.2 Risk factors for osteoporosis

As defined by the WHO, osteoporosis means that an individual has low bone mineral density measured by X-ray. Bone density is usually measured at the hip, lumbar spine or wrist. If the individual's bone density is lower than 2.5 standard deviations below the mean for 20-year-

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[3] Kanis et al., 2002.

olds, the individual is deemed to be suffering from osteoporosis. The diagnosis of osteoporosis does not in itself imply symptoms but means an elevated risk of the individual sustaining a fracture within a ten-year period. The fracture risk in itself is also strongly associated with several other risk factors discussed in more detail in the next subsection.

4.1.3 Risk factors for fractures

Fractures are due to a large number of different causes, and cadmium exposure may represent a risk factor. In the large review of risk factors and preventive medicine for fractures, both osteoporosis-related and non-osteoporosis-related fractures[4], by the Swedish Council on Technology Assessment in Health Care (SBU), it is noted that the important risk factors include:

- ***advanced age***
- ***low bone density***
- ***female gender***
- physical inactivity
- low weight (actually low BMI, *Body Mass Index*)
- ***smoking***
- high alcohol consumption
- neurological tendency to fall (dizziness etc.)
- impaired vision
- ***low exposure to sun***
- cortisone treatment
- genetic fractures (i.e. whether the parents have been affected by fractures)
- previous fall injuries
- other medical conditions

The risk factors listed in bold and italics are regarded as having an evidence-based association with osteoporosis. In American studies it is also emphasised that ethnicity may be an important factor in elevated fracture risk.

4.1.4 Who is affected by osteoporosis?

Osteoporosis and fractures affect elderly women in particular[5]. Among women over the age of 84, more than half suffer from osteoporosis and are therefore at increased risk of sustaining fractures. The amount of female sex hormone, oestrogen, decreases at the time of the menopause. Oestrogen has many functions, among other things contributing to the preservation of bone mass. When oestrogen production decreases, the breakdown of bone mass increases; bone mass decreases most during the first few years after menstruation has ceased.

Women with a higher proportion of body fat seem to have some protection against osteoporosis. This is due to the fact that even after the menopause women can produce an oestrogenic hormone from the male hormone androstenedione. This happens in the body's fatty tissue. A small and thin build person may therefore signify an increased risk of osteoporosis and also less protection in the event of a fall.

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[4] SBU, 2003
[5] SBU, 2003

Figure 2 below shows how the proportion of women suffering from osteoporosis increases with age.

Figure 2. Prevalence of osteoporosis in Sweden, proportion of women with osteoporosis at different ages. According to the WHO definition with T-score < -2.5 SD. [6]
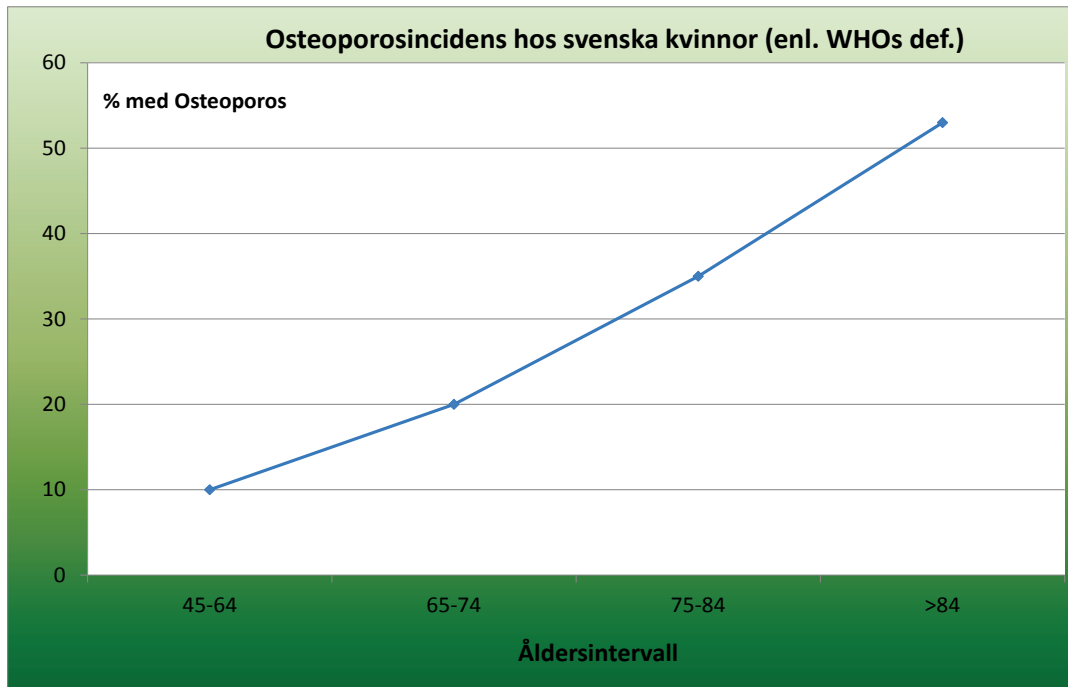
4.2 Cadmium fluxes

4.2.1 Health effects of cadmium

It was clarified long ago that very high exposure to cadmium can lead to multiple fractures: the disease "itai-itai", which was characterised by kidney damage, reduced bone mineralisation and osteoporosis[7]. Fifteen scientific studies, mainly from Sweden, Belgium and the United States, have since explored associations between considerably lower cadmium exposure and bone mineral density and/or osteoporosis. Most of these studies demonstrate associations between cadmium exposure – even at the relatively low levels that exist in the general population – and reduced bone density as well as increased risk of osteoporosis. In four of these studies, however, no statistically significant association has been observed between cadmium and low bone density, which leads to some uncertainty in interpretation. On closer examination of these four studies, it is noticeable that the null-findings could be due either to the study population being too small and, possibly too young individuals being included in the selection, or to over-adjustment in the statistical analyses. These studies therefore cannot be regarded as disproving an association.

Despite an association between low bone density/osteoporosis and elevated fracture risk being well established, the studies demonstrating a direct association between cadmium exposure

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[66] Borgström et al., 2006
[7] (Nordberg et al. 2007).

and increased risk of fractures represent an important piece of the puzzle and provide strong backing for cadmium exposure being linked to a substantial impact on public health[8].

The following aspects need to be considered regarding the relevant reference studies on which the calculations in this report are based:

1) Could the results be due to a spurious association that do not describe a causal relation? Most studies that have demonstrated associations between cadmium and the effects on bone have measured cadmium concentrations in urine, which provide an integrated measure of decades of exposure to the metal. The question is whether there is any other factor that could co-vary with the cadmium level in urine and that cause osteoporosis. Two studies, one with very high and one with significantly lower cadmium exposure, have, however, demonstrated associations between the cadmium measured in blood and reduced bone mineral density [9] – cadmium in blood reflects both recent and long-term exposure. In addition, some prospective studies that have demonstrated associations between cadmium and bone effects have used an estimate of dietary cadmium exposure by combining data from a questionnaire on individual dietary habits with data on the cadmium content of various foods[10] or have measured the cadmium level in soil or in vegetables grown in the participants' gardens[11]. Despite the risk of exposure misclassification (cadmium intake) being significantly greater in the use of diet surveys and the cadmium content of foods than when cadmium levels are measured in urine and blood, the studies show significant associations between estimated cadmium intake and increased risk of fractures. Furthermore, strikingly similar results were obtained when the cadmium concentration in urine was used instead of estimated exposure through dietary intake in the same women.

Overall, there is a low probability of the association between cadmium exposure and effects on bone in the general population being spurious, as it has been observed using three entirely different methods of exposure measurement (urine, blood and estimated dietary intake). Although the mechanism underlying the effect of cadmium on bone has not been fully clarified, experimental data support a causal association.

Smoking is what is known as a confounding factor that might interfere with the results, as tobacco smoke contains both cadmium and several other substances that may affect bone density or the risk of fracture. Some studies have, however, found a significant association between urine cadmium concentration or dietary cadmium intake and reduced bone density or fracture risk in individuals who have never smoked[12]. Two of these even show a stronger association for the group who have never smoked than for smokers or the whole group[13]. This could be explained by smoking making the biomarkers more uncertain as long-term markers. The findings provide backing for the hypothesis that the effect of cadmium on the skeleton is independent of smoking.

2) At what level of exposure does the effect on the skeleton arise? At present there is a lack of what is known as a meta-analysis, i.e. a weighted analysis which, if it is based on well conducted bone-effect studies, can provide a more reliable measure of the association/increase

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[8] Staessen et al. 1999; Wang et al. 2003; Alfvén et al. 2004; Engtröm et al. 2011; Engström et al. 2012; Thomas et al. 2011

[9] Alfven et al. 2002

[10] Based on Swedish data; Thomas et al. 2011; Engström et al. 2012

[11] in Belgium; Staessen et al. 1999

[12] Åkesson et al. 2006; Thomas et al. 2011; Engström et al. 2011; Engström et al. 2012

[13] Thomas et al., 2011; Engström et al, 2012

in risk. Such an analysis can then be used to clarify at what level of exposure the effects on the skeleton starts to occur. The reference studies (A1 and A2) are among the studies indicating associations between cadmium exposure and osteoporosis/fractures at the lowest level of exposure. The high quality of both cadmium analyses and bone density measurement (A1), as well as a large number of individuals and therefore high statistical power (A1 and A2) in the studies, probably contribute to this.

4.2.2   Cadmium uptake

The principal route of exposure to cadmium for the Swedish population is through foodstuffs, and the second largest is through smoking. In heavy and long-term smoking, the cadmium coming from tobacco smoke may account for half of the total cadmium burden on the kidneys. Dietary uptake of cadmium in the gastrointestinal tract is influenced by the form in which cadmium occurs in the food and the composition of the food.

There are also large individual differences, depending among other things on the individual's iron status; individuals with an iron deficiency have been shown to take up cadmium more effectively. Only a few per cent of the cadmium people ingest through food is usually taken up, but uptake can vary by up to around 10% in individuals with iron deficiency. Pregnant women and newborn infants and young children may have a higher uptake of cadmium in the intestine. Women of childbearing age are at great risk of being affected by iron deficiency, whereas this condition is not common in men. Studies in Sweden have shown that the incidence of iron deficiency may be high: 30% of women of childbearing age, but a higher incidence (50%) has also been shown in younger individuals (15 to 16-year-olds). The proportion of six-month-old infants with iron deficiency was 6%[14] [15]. Young children probably have a higher uptake of cadmium in the bowel than adults. Cadmium taken up from the intestine accumulates mainly in the kidneys. The half-life of cadmium is 10-30 years, which means that the level in the kidneys increases with age. The cadmium level measured in urine reflects the kidney accumulation, which is regarded as a good measure of the total body burden. The concentration of cadmium in the blood reflects recent exposure to a greater extent.

4.2.3   Limit values and tolerable weekly intake

The European Food Safety Authority (EFSA) expert group on toxicology, CONTAM, following a risk assessment of cadmium, has come up with a tolerable weekly intake (TWI) of 2.5 µg Cd/kg body weight, based on the detrimental effects of cadmium on the kidney[16]. In its assessment, EFSA came to the conclusion that the cadmium burden on the kidney should not exceed urinary cadmium concentrations exceeding 1 µg Cd/g creatinine. Scientific findings published since suggest associations between cadmium and increased risk of osteoporosis and fractures at urinary cadmium concentrations below 1 µg Cd/g creatinine.[17]

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[14] Hallberg et al., 1989
[15] Hallberg & Hulthén, 1992.
[16] EFSA, 2009
[17] Engström 2011, Gallagher, 2004

4.2.4 Cadmium in foodstuffs

The principal route of exposure for cadmium is through the diet and the foodstuffs that make the greatest contribution to cadmium intake in Sweden are cereals in bread (39%), leaf and root vegetables (25%) and potatoes (16%), see Figure 3. According to the dietary recommendations, the intake of wholegrain products, leaf and root vegetables should increase.

Figure 3. Proportion of cadmium intake from various foodstuffs, women aged 49-79, in 1997.[18]
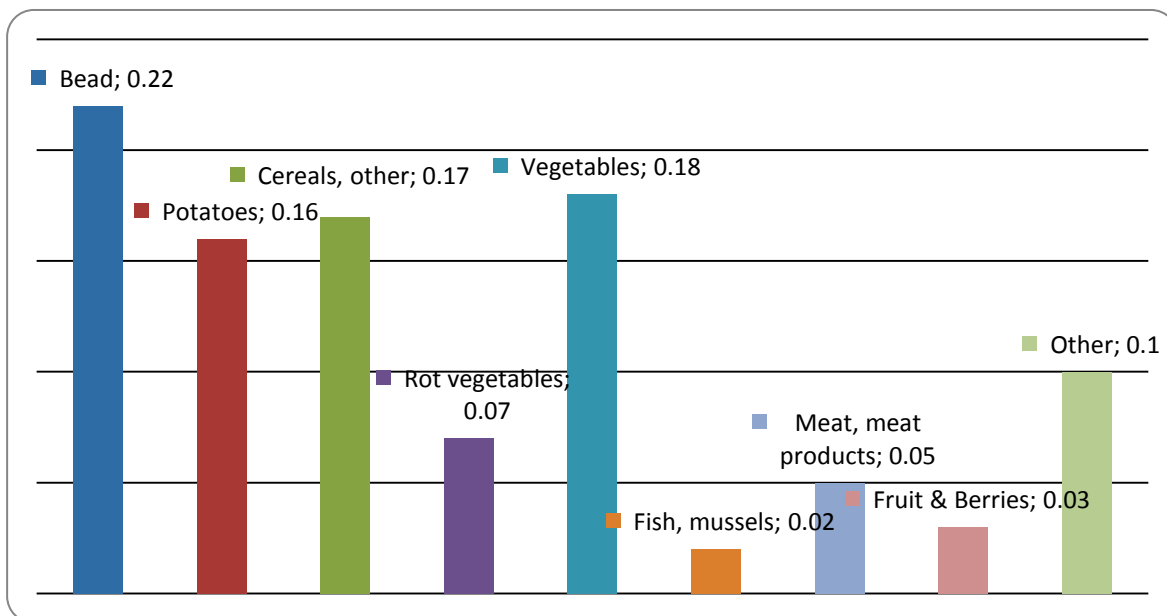
High levels of cadmium are found in the liver and kidney, in shellfish and in certain nuts and seeds. As these foodstuffs are not usually consumed frequently or in large amounts, however, their contribution to the average daily intake is smaller, which does not rule out the possibility that certain groups may have a high level of exposure from these foodstuffs. Eggs, milk and cheese usually contain low levels of cadmium.[19]

Average cadmium levels in a selection of foods are shown in Tables 1 and 2. It is possible to read from the statistics that individuals who eat a vegetable diet to a greater extent (vegans and vegetarians) have a higher cadmium intake than the normal population.

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[18] Julin, 2012.
[19] EFSA, 2009

Table 1. Cadmium levels in foods analysed by the Swedish National Food Agency.[20]

Type of foodstuff	Year	Number of samples	Mean level of cadmium, mg/kg fresh weight	EFSA or other EU limit values[21], mg/kg fresh weight
Milk	1998	20	<0.001	
Cheese	1995	23	0.002	
Fruit and vegetables	1996-97 2000-2002	146	0.018	0.05
Cereal products	1997-01	113	0.042	0.1 (0.2 for wheat)
Meat	1994-97	344	0.007	0.05
Liver and kidney	1994-99	460	2.56	0.5-1.0
Fish	1993, 2001	75	0.017	0.1
Egg	1998	5	<0.0007	
Potatoes	2000	75	0.010	0.1 (for peeled potato)

[20] Freely after KemI, 2011
[21] EC. 2006

Table 2. Cadmium levels in food samples analysed by the Swedish National Food Agency 1995-2008[22].

Type of foodstuff	Year	Mean level of cadmium, mg/kg fresh weight		
		All	Swedish	Imports
Cold meat products	1995	0.011	0.008	0.013
Fish fillet excluding eel	2001/2005	0.002	0.002	0.006
Eel	2001/2005	0.009	0.001	0.019
Cheese	1995	0.002	0.001	0.002
Wheat, spelt and rice products	2005/2007-2008	0.037	0.050	0.021
Pasta	1998	0.041	0.041	0.041
Root vegetables excluding potatoes	2005/2007-2008	-	0.016	-
Potatoes	2005/2007-2008	-	0.019	-
Spinach	2005	-	0.143	-

4.2.5 Smoking and cadmium

After foodstuffs, smoking is the principal route of exposure to cadmium for the Swedish population. The tobacco plant takes up cadmium to a great extent, and when the leaves are then dried and refined into various tobacco products, the cadmium level in the product increases (as the water content decreases). The smoker is exposed to the cadmium through the lungs, where the uptake kinetics is different than in absorption through the gastrointestinal tract; cadmium is taken up to around 50% in the airways[23]. This means that a person who smokes 15 to 20 cigarettes a day has a body burden of cadmium that is approximately twice as high as for non-smokers. Meta-studies have shown that smoking *de facto* can be associated with lower BMD and therefore increased risk of fracture[24].

4.2.6 Cadmium levels in nature and arable soil

Cadmium is found in surface water, groundwater, air and arable soil in Sweden, as it occurs naturally in the earth's crust. The mean level of cadmium in soil is regarded as 0.23 mg/kg dry matter[25], but varies from 0.08 to 0.5 mg/kg dry matter[26]. Cadmium in the environment may be

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[22] Freely after KemI, 2011
[23] WHO-ICPS, 1992
[24] Law & Bradshaw, 1997
[25] Eriksson et al., 1997.

either mobile and therefore bioavailable or be present in fixed form. What governs the bioavailability of cadmium is the pH of the water or soil[27] [28]. The lower the pH value of the soil is, that is to say the more acidic the soil, the more mobile and water-soluble cadmium becomes. In addition, readily mobile cadmium is taken up by all green plants in acidic soils. The levels of cadmium in Swedish arable soil are usually somewhat lower than in many European countries. Despite this, levels of cadmium in foodstuffs are not lower in Swedish-grown foodstuffs than in imported foodstuffs. This is due to the fact that Sweden has more acidic soils and softer water than many other European countries. The pH in Swedish soils is approximately one pH unit lower than in Central Europe; approximately 70% of cultivated land in Sweden has a pH value of less than 6.5, which is the limit for when the the soils should receive maintenance liming, and approximately 30% of soils have a pH of 6.0 or less[29]. The levels of cadmium in wheat are also comparable between Sweden and many other European countries. These circumstances indicate that the uptake of cadmium from soil to crop may be somewhat higher in Sweden than in Central Europe[30].

4.2.7   Input of cadmium

The principal sources for input of cadmium to Swedish agricultural land are atmospheric deposition and various types of fertiliser in agriculture. The atmospheric deposition originates from the burning of fossil fuels and biofuels and from industry[31]. The cadmium reaching Sweden through atmospheric deposition, rain and snow quite often originates in Central Europe. In addition, there are point emissions of cadmium principally to air in Sweden from the metal, paper and wood fibre industries, as well as from the energy sector. The use of mineral fertiliser has historically been responsible for the greatest spread of cadmium to the Swedish environment, while atmospheric deposition now provides the largest input of cadmium[32].

A study[33] of cadmium deposition in the Uppsala district reveals that 87% of the input of cadmium to fields that have received an application of mineral fertiliser came from airborne cadmium, while this figure was 56 to 71% in fields that received an application of farmyard manure and 37 to 59% in fields to which sludge had been applied as a fertiliser.

4.2.8   Cadmium in fertilisers

There is a risk of the cadmium added to arable land through fertiliser applications being taken up in the plants and foodstuffs cultivated on the arable land or leaching out with precipitation and consequently reaching the groundwater or being carried onwards to lakes and watercourses.

Mineral fertilisers are usually manufactured from crude phosphate or the mineral apatite; the cadmium content of mineral fertiliser varies depending on the raw material. Apatite from the Kola Peninsula has a very low cadmium level (0.3 mg Cd/kg P_2O_5), while crude phosphate

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[26] McBride, 1994
[27] He and Singh, 1993
[28] Eriksson 1989
[29] Eriksson et al., 1997
[30] Kemi, 2011, Annex 4
[31] Anderson, 1992
[32] Eriksson, 2009
[33] Eriksson, 2009

from Taiba in Senegal contains around 200 mg Cd / kg P_2O_5, to give two examples[34][35]. The level of cadmium in mineral fertiliser thus varies by a factor of a thousand.

4.2.9 Cadmium in articles and products

With regard to cadmium in articles and products, which may contribute to further cadmium leakage at the end of their life cycle, the level of use was very high until regulations in the late 1970s prohibited or restricted the substance in most products, particularly surface-treated steel articles[36]. However, cadmium may continue to be used in nickel-cadmium batteries for certain purposes[37] and as a paint pigment in artist's and hobby paints[38]. Electronic products imported into Sweden may contain cadmium. The maximum permitted level is usually 0.01% by weight in homogeneous materials, but there are exceptions regulated in the EU's RoHS Directive[39].

4.2.10 Historical cadmium levels and economic policy instruments

Levels of cadmium in Swedish arable soil are estimated to have increased by around 33% in the past 100 years[40]. This means that the historical cadmium level is 75% of the present-day level.

The greatest contribution to the increase, around 55%, over time has been the use of mineral fertiliser. In the past ten years atmospheric deposition of cadmium has instead become a greater contributory factor to cadmium levels in Swedish arable soil. The metal is contained as an impurity in the phosphate used to produce commercial fertiliser. By reducing the level of cadmium in phosphorus fertiliser, the amount of cadmium entering arable soil has fallen sharply, by 54%, since the 2001/2002 growing season. Sales of phosphate fertiliser have decreased by 17% over the same period[41].

The types of mineral fertiliser that have come to dominate in Swedish agriculture (NPK and NP fertilisers) now have a very low cadmium content. The levels have fallen from 25 mg [42] cadmium per kilogram phosphorus to an average of 5 mg cadmium per kilogram phosphorus [43] today. A contributory cause was the environmental charge for phosphorus in commercial fertiliser introduced in 1988. The charge was in 1995-2009 substituted by a tax on the cadmium content in commercial fertiliser. The tax rate was SEK 30 for each gram of cadmium per tonne of phosphorus in excess of 5 grams Cd/tonne P.

Mineral fertiliser is not allowed to be sold in Sweden if the cadmium content is higher than 100 grams Cd/tonne P. There is no harmonised limit value for cadmium in mineral fertiliser in the EU, but the level in most products is between 50 and 210 grams cadmium/tonne P.

Other factors that affect the levels of cadmium in Swedish arable soil (and consequently the levels in Swedish crops) are the use of manure and digested or limed sludge as a fertiliser

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[34] Hyltén-Cavallius, 2010
[35] European Commission, 2000.
[36] KemI, 1998
[37] Swedish Environmental Protection Agency, 2007
[38] Weiss, 2006
[39] EC, 2002
[40] Andersson, 1992
[41] Statistics Sweden, 2011
[42] Swedish Government Official Reports (SOU), 2003.
[43] Eriksson, 2009.

application on arable land. The levels of cadmium in manure (7-17 grams Cd/tonne P)[44], to which imported feed may contribute, are usually higher than in the mineral fertiliser products that are used.

The cadmium levels in digested/limed sewage sludge from sewage treatment plants have been around 30 mg Cd/tonne P, but these levels are decreasing over time. To allow the quality of the produced sewage sludge to be certified according to the ReVAQ criteria for sludge, the sludge may contain no more than 35 mg Cd/tonne, the aim is for this limit value to be reduced to 17 mg Cd/tonne P by 2015. The Swedish Environmental Protection Agency has further proposed a limit value of 45 mg Cd/tonne P as the maximum level of cadmium at which the sludge can be used as fertiliser. Relevant sales data for fertilisers in Sweden are presented in Table 3 below.

At present it is estimated that 10-15% of Swedish arable soil is fertilised with digested ReVAQ-certified sewage sludge. In the same way as for mineral fertiliser, not all soils are allowed to be fertilised with sludge. Phosphorus-rich soils may only be fertilised with an application equivalent to 22 kg P/ha and year.

Table 3. Sales of fertilisers in tonnes, 2009/10 [45]

Fertiliser	Quantity sold in tonnes of phosphorus (P) in 2009/10
P (Adds phosphorus)	100
NP (Adds nitrogen and phosphorus)	1300
PK (Adds phosphorus and potassium)	700
NPK (Adds nitrogen, phosphorus and potassium)	7700
Total	9800

4.3 Health economics

In health economics costs and benefits in the area of health and medical care are analysed both by general economic methodology and using methods specially developed for the area.

The aim of health economics is to estimate the effects and costs, which the introduction of a new drug for example is assumed to lead to. However, the calculations may also relate to costs and effects that a specific disease causes to society. Effects in this context usually mean the number of life years or quality-adjusted life years.

A health-economic analysis may also include what are known as indirect costs, such as loss of production or the cost that arises when family members care for the patient at home.

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[44] Steinbeck et al, 1999.
[45] Swedish Board of Agriculture 2011.

4.3.1 Quality-adjusted life years (QALY)

Life years mean how many years of life a particular treatment, medicine or disease adds to someone's life or shortens it by. The healthcare system does not aim just to prolong people's lives but primarily to prolong the years in a person's life when this person enjoys good health. The term *Quality-Adjusted Life Years (QALY)* is therefore used. Quality-adjusted life years is a measure by which different medical actions can be weighed against each other. An entirely healthy person is regarded as having the value 1 and a person who is dead has the value 0. One year at full health is equivalent to 1 QALY. QALY can be calculated by the patient rating their health on a scale or this being done by the treating doctor.

4.3.2 Willingness to pay for a quality-adjusted life year

WTP, (*willingness-to-pay)* is used to calculate the economic benefit of a quality-adjusted life year. This means the individual's willingness to pay to be able to live more years in full health or for example another two years with health rated at 0.5. It is assumed in this study that willingness to pay for a quality-adjusted life year is around SEK 600 000. This assumption is discussed later, and an alternative value is used in a sensitivity analysis.

4.3.3 Quality-adjusted life years and fractures

Fractures cause great health-economic costs, firstly in the form of direct costs, for example of the treatment of the fracture, and secondly in the form of increased mortality and poorer health, which leads to fewer quality-adjusted life years. For many elderly people (and their families), hip fractures for example are associated with great suffering, long and uncertain rehabilitation and also limited possibility of living a free, independent life in old age.

4.4 Environmental economics[46]

Environmental economics deals with the interaction between the economic system and the environment, and with allocating limited resources. Environmental economics among other things strives to include environmental effects in economic calculations, which would otherwise not take account of these effects.

Environmental economic studies make clear the value of the environment to society, the business community and individuals. Environmental valuation and economic impact assessments are examples of important tools contributing to making correct decisions in environmental policy. Economic policy instruments in turn are an important tool in implementing environmental policy.

An explanation of why environmental problems in the form of emissions occur is that the price of polluting the environment through emissions does not reflect the full economic cost. It often does not cost anything for a firm to pollute the environment. Consequently it becomes economically worthwhile to continue to pollute instead of abating. This is commonly referred to as market failures, and can be explained by the impact on the environment often leading to external effects (which the market players do not need to take responsibility for) and environmental goods often being collective goods (non-exclusive and/or non-rival). Those who pollute the environment are to some extent affected by their own pollution but the total cost of that pollution is the sum of the perceived cost of the pollution for all individuals.

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[46] Freely after Swedish Environmental Protection Agency, 2011.

External effects

External effects are effects of a choice that an individual or a company makes but that does not affect the individual or company. At the same time, they have an impact on welfare of the society. External effects arise for example when a person's consumption affects another individual's benefit, or when a company's production affects the production capability of another company without permission or compensation.

An example of a negative external effect is when emissions from one company adversely affect production conditions for another company. The problem arises when whoever causes the external effect determines how much is to be produced and emitted without taking account of what effect this has on others, and therefore on society at large.

In the case of a company's emissions, the company's costs of production are lower than the actual cost to society of the production. The result is that the company produces more and emits more pollutants than is economically optimal.

Market failures

Environmental economics is largely concerned with correcting these market failures. This means both attempting to calculate the "correct" level of production and consumption and steering companies and private individuals towards reducing their emissions to a sustainable level.

In order to deal with the environmental problems that arise due to the market failures referred to above, the market needs to be steered. The state is made the representative owner of environmental assets and make up rules or assigns different prices to these assets. Such prices aught to reflect the socio-economic benefits or costs of using the resource when producing and consuming various articles.

Cadmium in food

In this study we are studying the environmental and economic costs that exposure to cadmium causes to society. The cadmium that ends up in food comes both from airborne pollutants and from the fertiliser used on our fields. The airborne pollutants are a classic example of a negative external environmental effect the polluter does not pay for. The emissions often originate from polluters abroad. Those who are affected are the consumers of the crops produced on the fields and the farmers whose arable land may lose value.

As the consumers do not have access to any information about how high the level of cadmium is in a single food package, it is very difficult to deselect foods with high levels of cadmium. Even if such information was available it would not be easy for consumers to avoid these foodstuffs. There are already a number of parameters to be taken into account when shopping food, such as price, fat content, nutritional value, taste, quality, any ecolabelling etc. Few consumers would have the time and opportunity to also take account of cadmium labelling. In other words, cadmium in food is a market imperfection that affects the consumers of foodstuffs.

5 Reference Studies A1+A2. Association between dietary cadmium and fractures

Studies of the association between cadmium exposure and effects on people's bone health are a relatively new area of research. It was not until 2011 that two very well conducted studies showed associations between dietary cadmium intake and increased number of fractures. Previous studies have shown associations between cadmium content in urine and risk of osteoporosis (low BMD in bone density measurements), and it has long been known that massive exposure to cadmium leads to a condition that has given rise to multiple fractures, for example 'itai-itai disease' (Toyoma in Japan).

An association is not regarded as clarified in medical epidemiological research until several independent studies can verify the result. Best available data are often used in economic analyses. This economic study is based on two Swedish population-based prospective studies that point to a clear association between dietary intake of cadmium and increased number of fractures:

- Reference study A1. Engström A. (2011) *Cadmium As A Risk Factor For Osteoporosis And Fractures In Women,* Academic thesis at Karolinska Institutet, which is based on the following two published articles:

1) Engström A, Michaëlsson K, Suwazono Y, Wolk A, Vahter M, Åkesson A. (2011) Long-term cadmium exposure and the association with bone mineral density and fractures in a population-based study among women. *J Bone Miner Res*. 26:486-95; 2011.

2) Engström A, Michaëlsson K, Vahter M, Julin B, Wolk A, Åkesson A. (2012) Associations between dietary cadmium exposure and bone mineral density and risk of osteoporosis and fractures among women. *Bone*. 50:1372-8.

- Reference study A2. Thomas, L DK, Michaëlsson K, Julin B, Wolk A and Åkesson A. *(2011)* Dietary Cadmium Exposure and fracture incidence Among Men: A population-Based Prospective Cohort Study*, J Bone Miner Res,* 7:1601-8, 2011.

5.1 How cadmium intake increases women's risk of fractures

Some key results from the thesis *Cadmium As A Risk Factor For Osteoporosis And Fractures In Women (reference study A1)* are presented here. This thesis studies the effects on bone health of long-term low level exposure to cadmium in Swedish women. The study relates to a population-based study on approximately 2,700 women aged 54 to 69. Cadmium exposure was assessed both through measurements of cadmium in the urine and by estimating the dietary intake of cadmium through a food frequency questionnaire linked to a database containing the cadmium contents of foodstuffs. The cadmium concentration in urine is a good proxy of long-term cadmium intake. The group of women studied was divided into two equally large groups (median split), one with lower dietary cadmium exposure and one with higher dietary cadmium exposure.

Table 4. Characteristic (mean) values for the women participating in the study on women[47]

	Group with low Cd exposure (n=1338)	Group with high Cd exposure (n=1338)
Dietary cadmium exposure (mean micrograms/day)	*11*	*15*
Age at time of sampling/measurement of bone density, years	*64*	*64*
Education, > 9 years %	*54*	*55*
BMI, Body mass index, kg/m^2	*24*	*24*
Ever taken postmenopausal hormones, %	*59*	*61*
Physical activity, MET hours/day	*41*	*42*
Never smokers , %	*44*	*47*
Alcohol consumption, g /day	*6.8*	*5.8*
Dietary calcium, mg/day	*1081*	*970*
Dietary magnesium, mg/day	*301*	*337*
Dietary iron, mg/ day	*9.9*	*12*
Dietary fibre, g/day	*19*	*24*

As can be seen from the table, the listed factors do not differ greatly between the women who have a high (above the median) and those who have a low dietary cadmium exposure (Table 4). Women with a high dietary exposure to cadmium generally eat somewhat more nutritious food than those with lower exposure as cadmium is often contained in nutritious food such as whole-grain products and vegetables. The estimates that are presented below and form the basis for our calculations have been adjusted using multivariable analysis with respect to the above factors. The results have also been merged with the results on the association between cadmium levels in urine and the risk of fractures. The combined results are shown in Table 5.

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[47] Engström, 2011

Table 5. Risk (odds ratio) of any first fracture in women with high cadmium intake through food (above the median) compared with women with low intake (below the median) during 11 years of follow-up.

	Women with low dietary cadmium exposure	Women with high dietary cadmium exposure
Average dietary cadmium exposure (µg /day)	11.0	15.0
Number of fractures	183	211
Odds ratio and 95% confidence interval for fractures where the risk in women with low intake is set at 1.*	1.00 (reference)	1.31 (1.02-1.69)

* Multivariable-adjusted analysis taking account of the factors in Table 3

5.2 How cadmium intake increases men's risk of fractures

The study *reference study A2,* examines how much the fracture risk increases for men with increased dietary intake of cadmium.

This study is based on 20 173 men and 2 183 fractures. Here too the results are adjusted using multivariable analysis to control for other factors such as age and smoking status, to minimise the possibility of the results pointing to associations other than that investigated.

Table 6. Relative risk of a first fracture for men in relation to the tertile with the lowest dietary cadmium exposure*.

	Men in the lowest tertile of dietary cadmium exposure	Men in the middle tertile of dietary cadmium exposure	Men in the highest tertile of dietary cadmium exposure
Number of fractures	724	709	750
Average dietary cadmium exposure (µg /day)	15.5	18.6	22.2
Relative risk and 95% confidence interval for fracture where the risk is set at 1 in men in the lowest tertile of cadmium intake.	1.0	1.09 (0.98-1.22)	1.19 (1.06-1.34)

* Multivariable-adjusted analysis taking account of around twenty different factors

The results of this study indicate that there is also an association between cadmium intake and a first fracture for men. The associations are well within the 95% confidence interval.

6 Reference study B. Economic costs of fractures

6.1 Fracture-related health care costs

To enable us to calculate how great an economic cost of fractures is caused by dietary cadmium, we need to know how great the total costs are. For this purpose we use

- Reference study B. Ström O, Borgström F, Kanis J A, Compston J, Cooper C, McCloskey E V and Jönsson B (2011) Osteoporosis: burden, health care provision and opportunities in the EU, *Arch Osteoporos, 1-2:59-155, 2011.*

. This study presents the health-economic costs of fractures in Sweden and in the five large EU Member States, Germany, the United Kingdom, Spain, Italy and France. For more detailed descriptions of how the calculations in reference study B have been performed, reference should be made directly to the report and the underlying studies it is based upon.

Reference study B takes account of fractures that arise in the over-50 age group. The report distinguishes between health care costs of treatment and social care that arise during the first year and health care costs arising after the first year. In addition, the costs of deaths, chronically reduced quality of life and functional impairment in the form of loss of quality-adjusted life years are presented. Administrative costs are also included.

Table 7. Economic costs of all fractures, irrespective of cause, in Sweden, millions of euros/year.

Short-term health care costs	Long-term health care costs	Administration etc.	Loss of quality-adjusted life years	Total
860	530	30	2 700	4 100

The costs of loss of quality-adjusted life years account for by far the greater part of the economic cost of fractures (see explanation in the background chapter of the report). The reason why the cost is so great is that fractures lead to increased mortality and therefore a great loss of life-years as well as to lower quality of life, which reduces the value, the quality, of the patient's remaining years of life.

7 Economic costs of fractures caused by cadmium

7.1 The association between dietary cadmium exposure and fractures

The calculations are based on data from both women and men produced at Karolinska Institutet. The increase in risk is based on a comparison between the risk above the median in cadmium intake and the risk below the median. The aetiological fraction , see the table below, is the part of the morbidity explained by a particular exposure[48]. In this case we estimate the proportion of fractures that can be explained by cadmium exposure through food. The formula for calculation is:

$$Aetiological\ fraction = p\ (RR - 1)/RR$$

where p is the prevalence of exposure among the cases, i.e. the number of cases in the exposed group divided by the total number of cases and RR is the relative risk. Both p and RR are obtained from studies A1 and A2, where RR is adjusted for a number of confounding factors.

Table 8. Basis of calculation for men (Study A2). Note that the relative risk is converted from three exposure levels (presented in Table 6 on page 34) to two levels (above and below the median).

	All
Number of fractures in the group with cadmium intake above the median	1115
Total number of fractures	2183
p, prevalence of exposure among cases	0.5108
RR (at a cadmium intake above compared with below the median)	1.153
Aetiological fraction; the proportion of the fracture cases that can be attributed to dietary exposure to cadmium.	6.78
95% CI of the aetiological fraction Lower (=5%)	2.4
95% CI of the aetiological fractionHigher (=95%)	10.9

Table 9. Basis of calculation for women (Study A1).

	All
Number of fractures in the group with cadmium intake above the median	211
Total number of fractures	394
p, prevalence of exposure among cases	0.5355
Odds ratio*	1.31
Aetiological fraction; the proportion of the fracture cases that can be attributed to dietary exposure to cadmium.	12.7
95% CI of the aetiological fraction Lower (=5%)	0.8
95% CI of the aetiological fraction Higher (=95%)	23

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[48] (Ahlbom et.al, Grunderna i Epidemiologi)

As the formula for the aetiological fraction is based on the relative risk (RR) and reference study A1 (but not A2) was based on the odds ratio, a sensitivity analysis was performed in which RR was estimated on unadjusted values and compared with the equivalent odds ratio to see whether RR deviates clearly from OR. RR (= the incidence in those with cadmium intake above the median/the incidence in those with cadmium intake below the median [a/(a+c)] / [b/(b+d)] = (211/1338)/(183/1338) = 1.15

OR according to a*d/b*c = 211*1155 / 183*1127 = 1.18. There is thus no major deviation (RR=1.15 vs OR=1.18), but a small suggestion of overestimation of the risk.

Calculation of the aetiological fraction is based on the assumptions that *i*) there is a causal relation between cadmium exposure and fractures (section 4.2.1) and *ii*) that the relationship between cadmium intake and increase in risk is fairly proportional at different intakes above the median. Both studies A1 and A2 provide support for a linear increase in the risk of fracture at increasing cadmium intake.

7.2 Economic costs of fractures due to dietary cadmium

The results of the various reference studies are combined in this section.

We have made some calculations in order to be able to distinguish between the costs for men and women as the proportions of all fractures that can be explained by dietary cadmium differ between the genders and because the relative distribution of the health care costs and quality-adjusted life years (QALYs) also varies with gender. 31% of the health care costs can be attributed to men and 69% to women. For quality-adjusted life years, men account for 33% of the costs, while women account for 67%. All the values have been converted from Euros to Swedish kronor at an exchange rate of 1:9. In aggregate terms, we obtain the results below.

Table 10. Economic costs of all fractures for women and men in Sweden, SEK million/year.

	Short-term health care costs	Long-term health care costs	Administra-tion etc.	Loss of quality-adjusted life years	Total
Men	2 500	1 600	79	8 900	13 000
Women	5 700	3 500	180	17,000	26,000
All	8 200	5 000	260	26 000	39 000

In the next stage we combine these results with the values presented by reference studies A1 and A2 on how great a proportion of the bone fractures of men and women is accounted for by dietary cadmium levels.

The result indicates that dietary cadmium intake would mean an annual economic cost of SEK 4.2 billion. As shown by the table below, the costs of deaths and suffering make up about two-thirds of the cost, while health care costs account for a third or SEK 1.46 billion.

Table 11. Economic costs of fractures caused by high dietary levels of cadmium, women and men in Sweden, SEK million/year.

	Short-term health care costs	Long-term health care costs	Administratio n etc.	Loss of quality-adjusted life years	Total
Men	170	100	5	600	880
Women	720	440	22	2100	3 300
All	890	540	28	2700	4 200

7.3 Sensitivity analysis

Table 12 presents the outcome of a sensitivity analysis of the result for extremity levels for the aetiological fraction in the 95% confidence interval. The analysis indicates that the interval for cost is relatively large.

Table 12. Sensitivity analysis given the lowest and highest aetiological fractions according to the 95% confidence interval (CI)

	Aetiological fraction; Proportion of the fracture cases that can be attributed to dietary exposure to cadmium.		Economic cost, SEK m
	Women	Men	
Calculated value	12.7	6.78	4 000
Lower CI (5%)	0.8	2.4	490
Upper CI (95%)	23	10.9	7 000

8 Sensitivity analysis for lower value of a QALY

The analysis is based on the estimate in reference study B that the value of a quality-adjusted life year (QALY) is approximately SEK 630 000 per year. This is on a par with older studies of people's willingness to pay to avoid fatal accidents in the area of road safety[49], The estimation of the cost of a life has doubled since that time[50]. This indicates that the value ought to be higher. On the other hand, the National Board of Health and Welfare's classification of cost per quality-adjusted life year is that SEK 650 000 is of the right order of magnitude, possibly somewhat high. The National Board of Health and Welfare indicates the range of SEK 100 000 to 500 000 per QALY as a *moderate cost* while SEK 500 000 to 1000 000 is regarded as a *high cost*. This suggests that the National Board of Health and Welfare regards SEK 500 000 per QALY as a guide value[51] A value of SEK 500 000 per QALY would affect the economic cost as shown in Table 13.

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[49] (SIKA, 2002)
[50] (SIKA, 2002) and (Swedish Transport Administration, 2009)
[51] (National Board of Health and Welfare, 2011)

Table 13. Sensitivity analysis, economic cost for differing value of a QALY

	Economic cost per year of fractures caused by cadmium, SEK million
QALY valued at approx. SEK 660 000	4 200
QALY valued at SEK 500 000	3 500

8.1 Discussion of the results

It has been found that those women and men who have a higher dietary intake of cadmium are at significantly greater risk of being affected by bone fractures than those who have lower intake. This applies after the results have been adjusted for a number of other factors, such as age and BMI etc.

These results have several strengths. They are based on Swedish data, which is important as Sweden differs from other countries with regard to the risk of fractures. The risk of fractures is very high in Sweden. Secondly the results are based on studies in which a relatively large number of individuals have been included. This applies to the study of men in particular. Thirdly the results in reference study A1 are supported by equivalent results for cadmium exposure determined in urine and by results for both cadmium intake and level in urine in relation to reduced bone density (measured by X-ray) and increased fracture risk in the same women. Fourthly the observed association is at least as clear in the group who have never smoked.

As described in section 7.1, the calculation is based on assumptions that there is a causal connection between cadmium exposure and fractures (see also section 4.2.1). At present there are no weighted data from several different studies, a 'meta-analysis', that provide a more reliable measure of the increase in risk given that the analysis is based on well conducted studies, which is a limitation. A weighted result can also provide a more reliable measure of the level of exposure regarded as safe, i.e. below which level adverse effects on bone probably do not occur. New studies of the association between cadmium and fractures are, however, desirable to further strengthen the results and to clarify correlations at low exposure.

The reference studies have somewhat different age ranges, although they all relate to persons in the older part of the population. It is difficult to say exactly how this influences the results, but we assume that exposure to cadmium in younger years also leads to an elevated risk of fractures in later years, due among other things to the fact that a person's dietary habits can be assumed to change slowly over time.

Reference studies A1 and A2 are cleared of individuals who have previously had a fracture. The material thus relates to persons who have had their first fracture, known as incidental cases. There is a risk of this underestimating the correlation between cadmium and fractures.

9 Conclusions

This report is principally based on the results of scientific studies, two medical and one health-economic study. The former show, among other things, that there is a statistically verified association between dietary cadmium exposure and increased risk of suffering fractures. The proportion of fractures that are due to cadmium being present in our diet is estimated at 13% for women and 7% for men. The health-economic study shows that the economic costs of fractures in persons over the age of 50 are SEK 39 billion per year in Sweden.

Calculations based on these studies show that the economic cost of fractures caused by high cadmium concentrations in food is roughly SEK 4.2 billion per year. Of this sum, health care costs total almost SEK 1.5 billion, while other costs are due to reduced quality of life and premature death among individuals who have suffered a fracture. This result confirms previous suspicions that the economic costs of cadmium in our diet are high.

The results show that from the point of view of society priority should be given to reducing the dietary exposure of the population to cadmium. This can be expected to lead to reduced health care costs and reduced suffering. It applies in particular to elderly women, who are more commonly affected by fractures. This should not be seen as an individual issue but further measures are required to reduce the flow of cadmium to arable soil through the air and various forms of fertiliser use.

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