The EFSA Journal (2004) 72, 1-24

Opinion of the Scientific Panel on Contaminants in the Food Chain on a request from the Commission related to cadmium as undesirable substance in animal feed

(Question N° EFSA-Q-2003-033)

Adopted on 2 June 2004

SUMMARY

Contamination of animal feed materials by cadmium cannot be entirely avoided given its prevalent occurrence in the environment. Current statutory maximum levels for feedstuffs successfully prevent toxic effects in farm animals. Dietary cadmium exposure affects the absorption of trace elements, particularly that of copper resulting in an apparent copper deficiency in ruminants. In turn, high copper supplementation of feeds for pigs was considered to comprise the risk of an undesirable cadmium accumulation in the liver and kidneys, whereas zinc supplementation of feed reduces cadmium bioavailability. Within the EU maximum levels have been set for trace elements in animal diets, including copper and zinc (Commission Regulation (EC) 1334/2003). If these permissible levels are not exceeded, the overall tissue burden of cadmium is unlikely to exceed the maximum levels set for foods from animal origin under the conditions of current agricultural practice. Ruminants and horses, however, may be exposed during their entire lifespan to cadmium present in pastures. In distinct regions, this may result in an undesirable cadmium accumulation particularly in kidneys. The frequent consumption of kidney tissue from older animals (cattle and horses), as well as the frequent consumption of liver and kidneys from wildlife may thus contribute significantly to the overall human exposure.

Key words: Cadmium, animal feeds, animal toxicity, feed supplements, residues.

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BACKGROUND

1. General Background

Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in animal feed[1] replaces since 1 August 2003 Council Directive 1999/29/EC of 22 April 1999 on the undesirable substances and products in animal nutrition[2].

The main modifications can be summarised as follows

- extension of the scope of the Directive to include the possibility of establishing maximum limits for undesirable substances in feed additives.
- deletion of the existing possibility to dilute contaminated feed materials instead of decontamination or destruction (introduction of the principle of non-dilution).
- deletion of the possibility for derogation of the maximum limits for particular local reasons.
- introduction the possibility of the establishment of an action threshold triggering an investigation to identify the source of contamination ("early warning system") and to take measures to reduce or eliminate the contamination ("pro-active approach").

In particular the introduction of the principle of non-dilution is an important and far- reaching measure. In order to protect public and animal health, it is important that the overall contamination of the food and feed chain is reduced to a level as low as reasonably achievable providing a high level of public health and animal health protection. The deletion of the possibility of dilution is a powerful mean to stimulate all operators throughout the chain to apply the necessary prevention measures to avoid contamination as much as possible. The prohibition of dilution accompanied with the necessary control measures will effectively contribute to safer feed.

During the discussions in view of the adoption of Directive 2002/32/EC the Commission made the commitment to review the provisions laid down in Annex I on the basis of updated scientific risk assessments and taking into account the prohibition of any dilution of contaminated non-complying products intended for animal feed. The Commission has therefore requested the Scientific Committee on Animal Nutrition (SCAN) in March 2001 to provide these updated scientific risk assessments in order to enable the Commission to finalise this review as soon as possible (Question 121 on undesirable substances in feed)[3].

It is worthwhile to note that Council Directive 1999/29/EC is a legal consolidation of Council Directive 74/63/EEC of 17 December 1973 on the undesirable substances in animal nutrition[4], which has been frequently and substantially amended. Consequently, several of the provisions of the Annex to Directive 2002/32/EC date back from 1973.

[1] OJ L140, 30.5.2002, p. 10
[2] OJ L 115, 4.5.1999, p. 32
[3] Summary record of the 135th SCAN Plenary meeting, Brussels, 21-22 March 2001, point 8 – New questions (http://europa.eu.int/comm/food/fs/sc/scan/out61_en.pdf)
[4] OJ L 38, 11.2.1974, p. 31

The opinion on undesirable substances in feed, adopted by SCAN on 20 February 2003 and updated on 25 April 2003[5] provides a comprehensive overview on the possible risks for animal and public health as the consequence of the presence of undesirable substances in animal feed.

On the basis of this opinion, some provisional amendments are proposed to the Annex of Directive 2002/32/EC in order to guarantee the supply of some essential, valuable feed materials as the level of an undesirable substance in some feed materials, due to normal background contamination, is in the range of or exceeds the maximum level laid down in the Annex I of Directive 2002/32/EC. Also some inconsistencies in the provisions of the Annex have been observed.

It was nevertheless acknowledged by SCAN itself for several undesirable substances and by the Standing Committee on the Food Chain and Animal Health that additional detailed risks assessments are necessary to enable a complete review of the provisions in the Annex.

2. Specific Background

SCAN concluded[6] that the ions and elements, including cadmium, listed in Council Directive 1999/29/EC are commonly encountered substances with known toxicity. In each case, the contribution of food products of animal origin to the human exposure is limited and listing of these elements as undesirable substance in feed, although concomitantly contributing to an overall reduction of human exposure to toxic forms, is mainly justified by reasons of animal health.

A detailed risk assessment of the presence of cadmium in animal feed and the possible effects for animal health and public health is necessary and urgent as it appears that cadmium present at the maximum levels established in legislation for cadmium may affect the health of pigs and consequently a complete review of the maximum levels for cadmium on the basis of a detailed risk assessment is urgently necessary.

TERMS OF REFERENCE

The European Commission requests the EFSA to provide a scientific opinion on the presence of cadmium in animal feed.

This detailed scientific opinion should comprise the

- determination of the toxic exposure levels (daily exposure) of cadmium for the different animal species of relevance (difference in sensitivity between animal species) above which signs of toxicity can be observed (animal health / impact on animal health)
- the level of transfer/carry over of cadmium from the feed to the products of animal origin that results in unacceptable levels of cadmium in the products of animal origin in view of providing a high level of public health protection.
- identification of feed materials that could be considered as sources of contamination by cadmium

[5] Opinion of the Scientific Committee on Animal Nutrition on Undesirable Substances in Feed, adopted on 20 February 2003, updated on 25 April 2003 (http://europa.eu.int/comm/food/fs/sc/scan/out126_bis_en.pdf)

[6] Opinion of the Scientific Committee on Animal Nutrition on Undesirable Substances in Feed, point 6.11. Conclusions and recommendations.

- characterisation, insofar as possible, of the distribution of levels of contamination
- assessment of the contribution of the different identified feed materials as sources of contamination by cadmium
  - to the overall exposure of the different relevant animal species to cadmium,
  - to the impact on animal health
  - to the contamination of food of animal origin (the impact on public health), taking into account dietary variations and variable carry over rates (bio-availability) depending on the nature of the different feed materials[7].
- identification of possible gaps in the available data which need to be filled in order to complete the evaluation.

ASSESSMENT

1. Introduction

Cadmium (Cd) occurs naturally in the environment (in its inorganic form Cd^{2+}) as a result of volcanic emissions and weathering of rocks. In addition, anthropogenic sources have increased the background levels of cadmium in soil, water and living organisms. Cadmium is released into the environment by wastewater, waste incineration, and diffuse pollution of agricultural soils is caused by the use of fertilisers, which may contain cadmium at variable concentration depending of their origin (WHO-IPCS, 1992, Nordic Council, 2003). Within the biosphere, different processes may translocate cadmium over large distances and regional emissions (non-ferrous metal production, combustion of oil products, waste incineration) may account for the contamination of entire regions.

Atmospheric deposition of cadmium results in contamination of the topsoil. Indeed, cadmium balances for farmland in Denmark, Sweden and The Netherlands confirmed the accumulation of atmospheric cadmium in soils. Together, with sludge and commercial fertilizers, this atmospheric deposition seems to be the dominant source of farmland contamination. A risk assessment undertaken by several European countries substantiated the linear relationship between the amount of phosphate fertilizers used and the local cadmium deposition in the soil surface. Subsequently, the local cadmium burden varied in accordance to the permissible cadmium levels in these phosphate fertilizers (Bodganovic *et al*., 1999; McBride 1998). In many regions, however, the cadmium input from phosphate fertilizers is declining, due to legal restrictions in their application.

Higher concentrations of cadmium in soils have also been reported following the application of sewage sludge and farmyard manure, which contain variable and occasionally excessive cadmium concentrations (Bergkvist *et al*., 2003; Eriksson, 2000, Steineck *et al*., 1999). In addition, soils may become contaminated following dispersal of wastes from mining, or industrial processes associated with the smelting of metals such as zinc or lead (Koh and Judson, 1986; Spierenburg *et al*., 1988). Since cadmium is retained in the topsoil, concentrations can increase rapidly if the application of these materials to soil continues over long periods.

[7] Importance of the human exposure to cadmium from foods of animal origin compared to overall human dietary cadmium exposure can be assessed making use of the information contained in the report on a task on human exposure assessment to cadmium which has been recently performed at EU level within the framework of co-operation by Member States in the scientific examination of questions related to food (SCOOP – Task 3.2.11).

Increases in cadmium levels in soil result in an increase in the uptake of cadmium by plants (Lund *et al*., 1981; Van Bruwaene *et al.*, 1984), although the extent to which this happens will depend on the soil pH, plant species and the part of the plant (Sillanpää and Jansson, 1993; Eriksson, 2000). Uptake from soil is greater at low pH, and therefore processes that acidify soil (e.g. acid rain) will increase the cadmium concentrations in feeds and foodstuffs (IPCS, 1992). Conversely, increasing the soil pH of pastures by liming can reduce uptake of cadmium by grazing livestock (Eriksson *et al*, 1996; Morecombe *et al.*, 1994, Puschenreiter and Horak, 2000).

Cadmium exerts a variety of toxic effects including nephrotoxicity, osteoporosis, neurotoxicity, carcinogenicity[8] and genotoxicity, teratogenicity, and endocrine and reproductive effects (for review see IPCS, 1992; IHCP, 2003).

Upon absorption, cadmium is bound with high affinity to metallothionein (MT), initially denoted as Cd-binding protein. The actual level of MT (which is induced by cadmium) in individual tissues, and, in turn the remaining free cadmium fraction determines the cellular toxicity (Ju and Nordberg, 1998). The Cd-MT complex represents the major transport form of cadmium in the organism, but cadmium may be released from MT by lysosomal enzymes. Particularly in proximal tubule cells, this mechanism results in an increase in free cadmium. Free cadmium readily binds to other macromolecules including calmodulin. Interaction with calmodulin signalling pathways and disturbance of intracellular Ca^{2+} homeostasis seems to account for many of the clinically observed toxicities of cadmium, including renal proximal tubule injury and tubular cell necrosis (Brzóska and Moniuszko-Jakoniuk, 1998). Exposure to cadmium may also induce oxidative stress, which occurs secondary to the immediate cadmium toxicity, and includes lipid peroxidation and DNA single strand breaks (Goering *et al.*, 1993).

Kidney damage is the primary effect of cadmium exposure, associated with an impairment of the calcium and vitamin D metabolism and subsequent loss of bone mass, which may progress into osteoporosis in humans. Long-term administration affects not only renal function, but also the liver and the haematopoietic, immune, cardiovascular and skeletal systems (WHO-IPCS, 1992). Cadmium may interact with other trace elements and, in turn, the dietary levels of trace elements interfere with cadmium absorption and toxicity (see below) (Gupka and Gupka, 1998).

The Scientific Committee of Food (SCF) expressed an opinion on cadmium in June 1995 (SCF, 1995), in which it was stated that a carcinogenic risk from dietary exposure to cadmium, could not be excluded. While genotoxicity is well documented, other evidence suggest indirect modes of action.

The FAO/WHO Joint Expert Committee of Food Additives and Contaminants (JECFA) has established a provisional tolerable weekly intake (PTWI) of 7 μg/kg body weight (WHO, 2001), which was recently confirmed (WHO, 2003) and which is based on the evaluation of an early biomarker of renal damage following low dose cadmium exposure. This PTWI value corresponds to a daily intake of 60 μg of cadmium for the average person of 60 kg bodyweight.

2. Methods of analysis and statutory limits

Total cadmium concentrations in feeds and foodstuffs are commonly determined by electrothermal atomic absorption spectrometry (ETAAS). The method was validated for foodstuffs in a collaborative test by NMKL (Jorhem and Engman, 2000) in accordance with AOAC-Guidelines for collaborative study procedure (AOAC 1995). This method was also adopted

[8] Carcinogenicity has been only observed after inhalation and subsequently cadmium has been allocated to group 1 by the International Agency for Research on Cancer (IARC, 1993).

by CEN/TC275 (prEN 14084)[9]. An alternative pressure digestion procedure preceding ETAAS analysis has recently been developed (prEN 14083)[10] and validated in a collaborative study according to ISO 5725 (ISO 1994). The limits of detection/limits of quantification of these methods are well below the statutory limits set for food and feeds.

The current EU maximum levels for **cadmium in feed materials** are given in Table 1.

Table 1. Prescribed limits for cadmium in feedingstuffs, mg/kg, at a moisture content of 12%[11]

	Maximum content[12]
Feed materials of vegetable origin	1
Feed materials of animal origin	2
Phosphates	10
Complete feedingstuffs for cattle, sheep and goats[13]	1
Other complete feedingstuffs	0.5
Mineral feedingstuffs	5
Other complementary feedingstuffs for cattle, sheep and goats	0.5

For **food**, the maximum level of cadmium in meat of bovine animals, sheep, pig and poultry is 0.05 mg/kg, for horsemeat 0.2 mg/kg, for liver of cattle, sheep, pig and poultry 0.5 mg/kg, for kidney of cattle, sheep, pig and poultry 1,0 mg/kg, for fish 0.05 mg/kg or 0.1 mg/kg depending on the species, for other seafood 0.5 or 1.0 mg/kg, again depending on the species. In addition, maximum levels for wheat, rice, bran and germs is 0.2 mg/kg, for other cereals 0.1 mg/kg, for soybeans 0.2 mg/kg, for leafy vegetables 0.2 mg/kg, for stem and root vegetables and potatoes 0.1 mg/kg, for all other vegetables and fruits 0.05 mg/kg (EC, 2001).

3. Occurrence of cadmium in feed materials and animal exposure

Mean concentrations of cadmium in soils of ~ 0.5 mg cadmium/kg dry matters have been published in a number of countries (Underwood and Suttle, 1999). The uptake of cadmium by plants is variable, and the concentration in forages and crops grown on non-contaminated soils remains usually below 1.0 mg Cd/kg dry matter.

Data of the occurrence of cadmium in feed materials have been provided by a number of individual EU Member States or taken from reports published within the EU. Some of these data are difficult to evaluate because of limited information on the nature of the samples (e.g. compound feed without any detailed information on designated species) or inadequate sample

[9] Determination of lead, cadmium, zinc, copper and iron by atomic absorption spectrometry (AAS) after microwave digestion.
[10] Determination of lead, cadmium, chromium and molybdenum by graphite furnace atomic absorption spectrometry (GFAAS) after pressure digestion.
[11] Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in animal feed – L 140, 30.5.2002. as last amended by Commissions Directive 2003/100 EC of 31 October 2003, L 285, 1.11.2003
[12] In mg/kg of feedingstuff referred to a moisture content of 12%
[13] With the exception of complete feedingstuffs for calves, lambs and kids

description. The data that can reliably be categorised are summarised for forages and other feed materials in Table 2, and for commercially manufactured compound feeds in Table 3[14].

Table 2. Cadmium concentrations (mg/kg dry matter) in forages[15] and other feed materials.

	Mean	SD	Median	Min	Max	n =
Barley	0.11	0.12	0.08	0.02	0.29	6
Citrus pulp	0.19	0.22	0.10	0.02	0.50	10
Fish meal	0.40	0.37	0.21	0.04	1.4	44
Maize grain and maize by-products	0.06	0.14	0.01	0.01	0.50	29
Rapeseed, extracted	0.15	0.16	0.10	0.02	0.50	20
Soya bean meal	0.07	0.06	0.03	0.01	0.20	17
Sugar beet pulp	0.14	0.16	0.09	0.01	0.36	12
Sunflower meal	0.41	0.42	0.27	0.05	1.80	32
Wheat and wheat by-products	0.19	0.19	0.13	0.05	0.75	27
Grass/herbage (fresh)	0.62	Not determined (see footnote 14)				1217
Hay	0.73					950
Silage – grass	0.09					244
Silage – maize	0.28					345
All forage[16]	0.32					2761

The maximum permitted contents of cadmium in feed materials of vegetable and animal origins are 1.14 and 2.27 mg/kg dry matter, respectively[17]. While the data for feed materials are derived from a relatively low number of samples, there is no evidence that maximum permitted levels are being exceeded.

In these data, the concentrations of cadmium in forage crops are generally higher than in concentrate feed materials. Since concentration in forages grown on non-contaminated soils are generally low, the elevated levels may reflect crops that have been grown on soil to which high levels of cadmium have been added. As mentioned before, the main exogenous sources of cadmium are superphosphate fertilisers and sewage sludges (McBride, 1998). EC Directives aim to restrict the accumulation of cadmium in soils where sewage sludge has been applied to < 3 mg/kg dry matter at a depth of 20 cm.

Plants grown on soil that has been exposed to high applications of either (or both) of these sources, may contain elevated cadmium concentrations, particularly where they have been grown on acidic, sandy soils. A number of studies have examined the effects of sewage sludge application or the proximity to industrial processes on the cadmium content of forages.

[14] Where data have been reported as being below the level of detection, e.g. < 0.1 mg/kg, a value of half of the level of detection (in this case (0.05 mg/kg) has been used in calculating the mean and standard deviation.

[15] Some of the data for forages have been taken from reports in which only mean values have been reported. It has therefore not been possible to calculate standard deviations of the means, or medians, for forages or to report minimum/maximum values.

[16] Includes other forages not included in categories above.

[17] Directive 2002/32/EC gives maximum permitted levels of 1 and 2 mg/kg, for feeds of vegetable and animal origin, respectively, at a moisture content of 12%.

Richardson (1980) reported levels of up to 2.3 mg/kg dry matter, following application of sewage sludge, while levels of 15.8 mg/kg dry matter were observed in herbage growing adjacent to an industrial iron smelting plant (ADAS, 1991). Data from these studies have not been included in Table 2. In addition, the processes of harvesting herbage for conservation as hay or silage often result in soil being picked up with the crops, and therefore higher levels of cadmium may reflect soil contamination of the material being analysed.

Table 3. Mean concentrations of cadmium (mg/kg dry matter) in commercial compound feeds for farm livestock and fish (data reported by EU member states)[18,19]

Compound feeds	Mean	SD	Median	Min	Max	n=
Poultry – unspecified	0.16	0.12	0.16	0.01	0.4	33
Poultry – Layers	0.16	0.18	0.11	0.01	0.6	12
Poultry – Broilers	0.19	0.13	0.16	0.1	0.5	8
Fish	0.17	0.09	0.14	0.04	0.54	207
Pigs < 17 weeks	0.16	0.16	0.10	0.04	0.50	14
Pigs > 16 weeks	0.07	0.03	0.05	0.05	0.13	10
Pigs – unspecified	0.09	0.10	0.07	0.01	0.5	150
Pigs (sows)	0.09	0.061	0.09	0.03	0.16	4
Compound feeds – Ruminants[20]	0.11	0.06	0.11	0.03	0.85	358

In addition, some Member States provided data on mineral supplements and pre-mixtures. The mean value of all these samples was 0.58 mg/kg, and ranged from < 0.01 to 2.34 mg/kg dry matter[21]. The significance of high values in terms of exposure to livestock is difficult to establish, since these products are included in diets at varying inclusion rates.

Exposure of animals to cadmium results from the intake of feeds and is a function of the concentration of cadmium in the feed, and the amount of feed consumed. Moreover, uptake of soil during grazing (or soil contaminated feeds) is an additional factor contributing to total exposure of individual animals. In order to estimate the intake of, and level of exposure to cadmium, it is necessary to have estimates of both the likely intake (g or kg of dry matter per day) for each class of livestock, and typical dietary concentrations.

In estimating dietary exposure to cadmium, two approaches were considered. The first was to describe typical inclusion rates for feed materials used in the manufacture of compound feeds, and to calculate the final cadmium concentrations. However, this approach had to be rejected, primarily because information on many individual raw materials was scarce or not available. The alternative approach was to use data for manufactured compound feeds. This is the approach that was used previously by SCAN in its reviews of zinc and copper, and it has been adopted in this report.

For the majority of non-ruminant livestock (pigs and poultry as well as farmed fish) in the EU, feed is provided as compounded feed, consisting of a mixture of individual feed components, to

[18] Data obtained as part of routine surveillance of feed materials, and provided by Member States.
[19] No data on horse feed has been provided.
[20] Complete feeding stuffs and complementary feeds.
[21] Maximum permitted concentration for mineral feedingstuffs is 5 mg/kg (Directive 2002/32/EC).

which additives and/or mineral supplements are added. Intake of cadmium may therefore be estimated by multiplying the concentrations given in Table 3 by the estimated intake of the compound for the particular class of livestock. In Directive 2002/32/EC, the maximum permitted content of complete feeds for pigs, poultry and fish is 0.5 mg/kg (at a moisture content of 12%)[22]. In over 300 samples of compound feeds for fish, pigs and poultry, only two samples of compound fish feed exceeded this limit.

Estimating intake by ruminants is less straightforward. For cattle and sheep, the daily ration usually consists of forage (or mixture of forages), either fresh or conserved, together with complementary feeds or individual feed materials as necessary to achieve the required the level of production (growth rate, milk yield). The ratio of concentrate feeds to forage in the diet is also influenced by the digestibility of the forage. As discussed above, the *apparent* concentration of cadmium in herbage is frequently higher than in concentrates. It is not possible to establish from the information available whether these are inherent concentrations reflecting levels normally present in plant materials, or are the result of spurious contamination. The latter could arise either from the use of fertilisers or sewage sludge containing high concentrations of cadmium, or from direct soil contamination (see introduction).

For ruminants, Directive 2002/32/EC sets the maximum permitted cadmium contents at 1.0 and 0.5 mg/kg in complete feeding stuffs and complementary feeding stuffs, respectively (at a moisture content of 12%). For the compound and complementary feeds reported, none exceeded these limits, and in most cases were considerably lower than the given permissible levels. However, dietary concentrations for ruminant livestock (and horses) are most likely exceeding maximum levels permitted where the diet consists entirely of forage, and where the forage is 'contaminated'. As discussed above, this is most frequently seen on pastures to which sewage sludge has been applied (Baxter *et al*., 1983).

4. Adverse effects on livestock and exposure-response relationship

In general, clinical symptoms of cadmium toxicity in animals include kidney and liver damage, anaemia, retarded testicular development or degeneration, enlarged joints, scaly skin, and reduced growth and increased mortality (Neathery *et al*., 1975, Puls, 1994). Manifestation of toxicity varies considerably, as depending on dose and time of exposure, species, gender and environmental and nutritional factors. Subsequently, large differences exist between the effects of a single exposure to a high concentration of cadmium, and chronic exposures to lower doses (NRC, 1980, Kostial, 1986).

Many of the data on the toxicity for animals refer to studies in which relatively high doses were administered parenterally or orally for a short period. However, of much greater importance are studies that investigated the adverse health effects related to chronic exposure at levels regularly occurring in feeds. In most of the domestic animal species, it is assumed that 5 mg/kg dietary cadmium (5 mg Cd/kg feed) is the level at which gross clinical symptoms are most likely to commence, provided an otherwise adequate diet is offered (NRC, 1980, Kostial, 1986). However, minimum toxic levels or maximum safe dietary concentrations cannot be estimated with any precision, since cadmium disposition is significantly influenced by dietary interactions with zinc, copper, iron and calcium. Thus, in some cases, concentrations of cadmium as low as 1 mg/kg in the diet or drinking water did induce adverse effects in animals. These effects included renal function impairment, hypertension, disturbance of trace mineral metabolism (copper, zinc and manganese), and acute degenerative damage in the intestinal villi.

In horses, at concentrations exceeding 5 mg per kg feed cadmium slowly affects the re-absorption capacity for calcium and other substances in the kidneys resulting in calcium

[22] Note that values reported in tables 1 and 2 are expressed on a dry matter basis.

deficiencies. Tubular damage may occur and progress into impairment of glomerular filtration capacity, indicated by proteinuria. Furthermore, a long-term cadmium exposure may lead to reproduction disorders, hypertension, and a secondary copper deficiency with corresponding copper deficiency symptoms (Anke *et al.*, 1989).

In cattle, which have been chronically exposed to cadmium, various clinical abnormalities such as loss of appetite, renal failure, hypertension, anaemia, growth retardation, impaired reproductive function, abortions, teratogenic lesions, and tumour development has been reported from field cases and anecdotal reports on individual intoxications (Venugopal and Luckey, 1978; Wentink *et al.*, 1988).

In sheep, early signs of liver cell degeneration (greatly enlarged and swollen mitochondria and necrosis) were seen by electron microscopy following consumption of corn silage with a cadmium content of 1.7 mg/kg dry matter (Heffron *et al.*, 1980). In contrast, no signs of toxicity according to biochemical and patho-morphological examinations were found in bulls fed concentrates and maize silage with a cadmium content in the total diet of 1.8 mg/kg dry matter (Vreman *et al.*, 1988).

In pigs, the most prominent clinical signs are growth retardation and microcytic, hypochromic anaemia (Osuna *et al.*, 1981). Experiments conducted to assess the effect of graded levels of cadmium in pigs (over the growth period from 8 to 90 kg live weight with cadmium levels ranging from 0.44 to 4.43 mg/kg dry matter) added as $CdCl_2$ or rock phosphate to the diets, generally failed to demonstrate a significant depression on performance, including daily weight gain, feed intake and feed conversion (King *et al.*, 1992). Pigs fed a ration formulated with contaminated sewage-sludge corn with a cadmium content of 0.56 mg/kg dry weight during a period of 56 days revealed no alterations in relative organ weight, microscopic pathology, clinical biochemistry, cardiac function and central nervous functions as compared to controls (0.10 mg/kg cadmium in the diet). However, lower hepatic iron and renal manganese concentrations were measured. Minor changes in the activity of hepatic microsomal oxidases, and in the number of red blood cells in the exposed animals could also be related to the decreased hepatic iron (Hansen and Hinesly, 1979). The impairment of hepatic microsomal oxidases (CYP450 enzymes) following cadmium exposure has been observed also in laboratory animal species, and is considered as an early marker of cadmium exposure in humans.

In laying hens, reduced egg production has been observed when birds were fed a soy isolate diet containing 3 mg cadmium/kg dry matter over a period of 2 months. However, a similar effect did not occur with a non-purified diet (Leach *et al.*, 1979, Prinbilincova and Marettova, 1996).

In fish, the reported toxic effects of cadmium include structural damage of the gills and kidneys, osmoregulatory disturbances and enzyme inhibition in the liver and kidney (Thophon *et al.*, 2002). Affected fish appear passive and show loss of appetite. Following long-term exposure, fish exhibits signs of abnormal behaviour such as uncoordinated, erratic swimming. Additional clinical signs of intoxication may include increased frequency of opercular movements, inability to maintain equilibrium and, in some cases, skin darkening (Bucke *et al.*, 1983; Karlsson–Norrgren, 1985). Dietary exposure of Atlantic salmon (*Salmo salar*) to cadmium concentrations up to 204 mg/kg dry weight for four months did not affect growth. However, increased enterocyte proliferation and apoptosis as well as elevated metallothionein levels in kidney, liver and gut were evident in fish exposed to 6.7 mg Cd/kg dry matter and above, indicating toxic exposure at this concentration (Berntssen *et al.*, 2000; Berntssen *et al.*, 2001). Reduced nutrient digestibility was evident in Atlantic salmon exposed to dietary concentrations of 22, 112 and 204 mg Cd/kg dry matter (Berntssen and Lundebye, 2001).

Cadmium intoxication in companion animals including dogs and cats are rarely reported, although the same toxic mechanisms as observed in other mammalian species can be expected. Exposure to these carnivorous species can be considered to be low, with the exception of hunting dogs, which might ingest higher amounts of cadmium as they are given internal organs of hunted game traditionally. Dogs being exposed to $CaCl_2$ via drinking water for a period

of 4 years as varying concentrations of cadmium, ranging from 0.5 to 10 ppm, exhibited dose-dependently mild tubular atrophy accompanied by an invasion of inflammatory cells. No acute signs of toxicity were observed (anonym, 1980).

Interaction between cadmium and other minerals

As mentioned above, other minerals influence absorption and tissue disposition of cadmium and *vice versa*. In ruminants, even low levels of cadmium in the diet have been shown to act as potent antagonist of copper metabolism. Heifers fed diets containing 1 and 5 mg/kg of cadmium (as $CdCl_2$) during the gestation period showed liver copper concentrations that were 40 % and 17 % lower, respectively, than that of control animals. Calves from these dams consuming cadmium at a level of 5 mg/kg feed had a 29 % and 43 % reduction, respectively, in liver copper and zinc concentrations. In the same calves, packed cell volume, haemoglobin concentration and serum copper were decreased by 17, 18 and 25 %, respectively, whereas serum zinc was increased (55 %). Moreover, 4 % and 13 % reduced serum sodium and potassium levels were observed, and blood urea nitrogen was increased by 63 % (Smith *et al*., 1991a).

Studies in pregnant ewes and their lambs (Mills and Dalgarno, 1972) have demonstrated that dietary cadmium concentrations ranging from 3.5 to 12 mg/kg dry matter (as $CdCl_2$) during the last trimester of pregnancy and lactation greatly reduced liver copper concentrations in the ewes. In the lambs, a significant reduction of plasma and liver copper concentrations occurred at the end of the experiment: 80 % of lambs had blood copper in the deficiency range (below 0.6 μg/ml) and liver copper decreased from 109 mg/kg (controls) to 29 mg/kg (exposed animals).

In pigs, a significant increase of cadmium accumulation in tissues could be observed when high dietary supplements of copper were used in commercial pig fattening rations (Rambeck *et al.*, 1991). For example, in pigs receiving a diet containing 1 mg/kg cadmium (given as $CdCl_2$), as well as 0, 50, 100 or 200 mg/kg copper (given as $CuSO_4$) for a period of 3 months, copper retention in all tissues increased in correlation to the copper content of the feed. When 200 mg copper were added per kg feed, cadmium concentrations in the liver and kidney were twice as high as in the control animals (Rothe *et al*., 1992). These findings seem to be associated with the extraordinary capacity of the pig liver to respond to cadmium exposure with a significant increase in metallothionein synthesis (Henry *et al*., 1994).

Interactions were observed also between cadmium and zinc in various living organisms, including ruminants. The effect of supplemental zinc (600 mg/kg) on the concentrations of cadmium in tissues of calves fed 50 mg/kg cadmium for 60 days was evaluated by Lamphere *et al.* (1984). The cadmium concentrations of blood, liver, kidney, cortex and muscle were significantly reduced by zinc treatment, suggesting that zinc supply may reduce cadmium absorption as demonstrated in laboratory animals (Brzoska and Moniuszko-Jakoniuk, 2001). In ewes which obtained cadmium orally via feed at levels of 2.5 mg/kg/day for 21 days, followed by 1.25 mg/kg/day for 31 days, and of which a second group obtained also lead (2.3 mg/kg/day for 52 days) or lead plus zinc (2.3 mg lead/kg/day and 3.5 mg zinc/kg/d for 52 days), the lead exposure enhanced the cadmium concentrations in all tissues and in milk (Houpert *et al.*, 1997). The co-administration of zinc limited this enhancement, but cadmium concentrations in tissues remained higher than those observed when cadmium was administered alone.

5. Toxicokinetics and tissue disposition

The toxicokinetics of cadmium strongly depend on the route of exposure, inhaled or ingested, and on the physiological and dietary status of the exposed organism. An extensive part of the literature deals with injected and inhaled cadmium; many of these findings, however, are not applicable in the assessment of the effects of dietary cadmium. Thus the following section focus on the kinetics of cadmium following oral application.

5.1. Absorption

The absorption of dietary (inorganic) cadmium varies depending on the cadmium concentration in individual feed materials, the animal species, time and frequency of exposure, age or state of development, and nutritional status of the animal. Moreover, concomitant exposure to other minerals, especially iron, zinc, copper and calcium (as motioned above) as well as ascorbic acid and cholecalciferol influence the rate of absorption. Studies with different animal species have shown that 0.5 to 7 % of the ingested cadmium is absorbed. The apparently lower absorption by laboratory animals (1-2 %) and ruminants (1 %), as compared to humans (3 - 7 %), may be more related to differences in the standard diets than to differences in physiological parameters (Anderson *et al*., 1992). Retention and absorption of cadmium in the gastrointestinal tract is higher in younger than in older animals (Eklund *et al*., 2001; Lee *et al*., 1996). Moreover, cadmium absorption is increased if dietary calcium is low (Washko and Cousins, 1976; Brzoska and Moniuszko-Jakoniuk, 1998) or in humans with iron-deficiencies (particular women) (Berglund *et al*., 1994; Vahter *et al*., 2002).

In a comparison of the rates of accumulation of cadmium ingested with food and water, Ruoff *et al.* (1994) found that the bioavailability of cadmium from food is not significantly different from the bioavailability of cadmium from drinking water when food and water are provided *ad libitum* and the cadmium dose is less than 4 mg/kg body weight. These findings suggest that the bioavailability of cadmium is influenced by the contents of the gastrointestinal tract rather than by the exposure medium.

Various feed ingredients, particularly phytic acid, can form metal-ion complexes, inhibiting the absorption of cadmium form the gastro-intestinal tract (Persson *et al*., 1998). In turn, microbial phytase, added to the diet, often increases the absorption of cadmium (Zacharias *et al*., 2001).

5.2. Distribution

Data from *in vivo* experiments show that following absorption, cadmium is transported to the liver where it is bound to metallothionein (MT) forming a Cd-MT complex, the main form found in animal tissues. Exposure to Cd^{2+} originating from cadmium salts such as $CdCl_2$ or $CdSO_4$, also results in binding to serum albumin. The conversion of Cd^{2+} to Cd-MT can occur already in the intestines, in the liver and in the lungs (particularly following inhalation). Circulating Cd-MT complexes reach the kidneys, where they are filtered by the glomerulus, and reabsorbed by the proximal tubule cells. Minor changes in the intracellular pH and lysosomal enzyme activity cleave the Cd-MT complex and the resulting free cadmium accumulates in the kidney.

Upon chronic exposure to low environmental cadmium levels, the largest fraction (50 - 75 %) of cadmium is found in the liver and kidney, with the renal cortex having the highest concentrations. With increasing exposure, a greater proportion of the body burden will be found in the liver (Scheuhammer, 1987). In spite of low concentrations of cadmium in muscles, bone and skin, these tissues may represent a significant contribution (20 %) to the body burden due to their mass. The placenta and mammary gland effectively limit cadmium transport into the foetus and milk; thus the concentrations in organs of the embryo, foetus or a newborn animal

are by three orders of magnitude lower than in the parent animal. Very little cadmium is transported into avian eggs (NRC, 1980; Kostial, 1986).

Dietary cadmium uptake in fish depends on the dose (Andersen *et al.*, 1992). Cadmium accumulates primarily in the viscera (intestine, liver and kidney) of fish (Kraal *et al.,* 1995), whereas the distribution into muscle tissue is limited (2 – 6 %) (Cincier *et al.,* 1998).

5.3. Excretion

The continuous (and inducible) synthesis of Cd-MT in the liver and kidneys (and other organs) traps cadmium in these organs, and limits its elimination. It has been estimated that only < 0.01 % of the body burden is excreted daily, to a large extent with urine, but also with bile, the gastrointestinal tract, saliva, the skin and sweat (Kostial, 1986). When renal damage has occurred, cadmium excretion with urine increases dramatically (Friberg *et al*., 1986). The biological half-life of cadmium is reported to be 10-30 years in kidney and 4.7 - 9.7 years in liver (IPCS 1992, EPA 1997). Following low level exposure (such as arises from natural levels of cadmium in the environment) the long half-life and the probable transfer of cadmium from other tissues to the kidney, results in an accumulation of cadmium in the kidneys during the entire life-span.

6. Carry over and tissue concentration

Experimental data demonstrate a linear relationship between dietary cadmium intake in livestock and cadmium deposition in tissues (liver and kidney) (King *et al*., 1992; Lee *et al*.,1996; Petersson *et al*, 1997; Linden, 2002). In the case of kidney, cadmium residues are also directly related to the duration of exposure. In the muscle, cadmium deposition is very low and independent of the level of dietary cadmium exposure. However, many variables among other's rate of absorption (see interactions with divalent ions), MT and iron status, influence tissue deposition, and need to be evaluated as well to improve the accuracy of predictions of the cadmium burden in animal tissues (Lee *et al*., 1996).

Cadmium residues in the liver and kidneys of cattle (López Alfonso *et al*., 2000), calves (Sharma *et al*., 1979; Vreman *et al*., 1988; Smith *et al*., 1991b), sheep (Sharma *et al*., 1979; Hill *et al*., 1998; Lee *et al*., 1996), swine (Sharma *et al*., 1979; Hansen and Hinesly, 1979; Linden *et al*., 1999), poultry (Leach *et al*., 1979) and fish (Berntssen *et al*., 2001) fed standard diets (< 0.5 mg Cd/kg dry matter) were in most cases below the EU maximum admissible levels for animal products (i.e. 0.05, 0.5 and 1 mg/kg fresh weigh for meat, liver and kidney respectively) (EC, 2001). With increasing dietary cadmium exposure (1 - 5 mg Cd/mg dry matter) cadmium residues in the liver and kidneys generally exceeded the cadmium permissible residues in all the farm animals and with diets containing > 5 mg Cd/mg dry matter cadmium residues were one order of magnitude above these limits.

7. Human dietary exposure

Cadmium exposure intake via food commodities is of public health concern, as long-term exposure to cadmium gives rise to accumulation of cadmium in the renal cortex with subsequent renal toxicity. The biological half-life of cadmium in the kidney varies between 10 and 30 years in humans. Daily cadmium intake with food of 0.14 – 0.26 mg per day for more than 50 years, or a cumulative intake of > 2000 mg cadmium may result in renal tubular dysfunction (IPCS, 1992).

In contaminated areas, cadmium exposure via concentration in food may be up to several hundred μg per day (table 3). Meat, fish and fruit generally contain cadmium levels of 0.005 – 0.01 mg/kg fresh weight. Many plant-derived foodstuffs contain higher cadmium concentrations, and a value of 0.025 mg/kg fresh weight is considered representative for cereals and root vegetables. Offal from adult animals and certain shellfish, however, contain even higher concentrations; values between 0.05 – 0.5 mg/kg fresh weight were reported (IPCS, 1992). These levels initially appear of concern. However, when taking into account that the daily intake of offal's is rather low, as compared to other foodstuffs, exposure levels are considered within an acceptable range. Moreover, in Europe, cadmium levels in offal's are lower, as compared to the WHO data (table 4). Thus, among all mentioned food commodities, only crustaceans and bivalves molluscs considerably exceed the recommended level. Moreover, fruits and vegetables may exceed the statutory level in certain polluted regions (Urieta *et al*., 1996).

In is noteworthy to mention, that organs (liver and kidney) of wildlife (deer, hare, wild boar) which professional hunters consume frequently in contrast to the overall population, may contain also high amounts of cadmium (0.06 – 0.75 μg Cd/g fresh weight) (Hecht, 1989). The high concentrations not only reflect the environmental burden, but also relate to the particular feeding habits of these animals.

Cadmium is extensively bound to metallothionein (MT) in animal tissues and thus human exposure from edible tissue of animals thus includes the exposure to the Cd-MT complex. Experimental studies indicate that ingested Cd-MT can be absorbed intact, but data on the rate of absorption are contradictory. Studies on animal given a single oral dose of cadmium in the form of Cd-MT, shellfish-Cd, or $CdCl_2$ have indicated similar extent of absorption of all three forms of Cd. Differences were, however, observed in the tissue distribution, with Cd-MT and shellfish-Cd being distributed preferentially to the kidneys. In contrast, when animals were given Cd-MT or shellfish-Cd with the diet or via gastric tube for several weeks, the concentrations of cadmium in liver and kidney were consistently lower than in animals exposed to similar doses of $CdCl_2$, indicating a lower absorption of Cd-MT (data summarized by Vahter *et al*., 2002). It has also been demonstrated in experimental studies that the bioavailability of cadmium from boiled crab hepatopancreas is slightly lower than that of cadmium from mushroom and inorganic cadmium ($CdCl_2$). Cadmium in crab hepatopancreas is mainly associated with denaturated proteins of low solubility, whereas a large fraction of Cd in dried mushrooms is associated with soluble ligands (Lind *et al*., 1995).

At its fifty-fifth meeting, the JECFA evaluated the dietary intake of cadmium using data from a number of countries. Estimates of the mean national intake of cadmium ranged from 0.7 - 6.3 μg/kg b.w. per week. Mean dietary intakes, derived from GEMS/Food regional diets (average per capita food consumption based on food balance sheets) and average concentrations of cadmium in these regions, range from 2.8 - 4.2 μg/kg b.w. per week. For some individuals, the estimated total intake of cadmium might exceed the PTWI of 7 μg/kg b.w. because total food consumption for high consumers is estimated to be about twice the mean. Regarding the major dietary sources of cadmium, the following foods contributed 10% or more to the PTWI in at least one of the GEMS/Food regions: rice, wheat, starchy roots/tubers, and molluscs. Vegetables (excluding leafy vegetables) contribute > 5 % to the PTWI in two regions.

In a recent SCOOP report (EC, 2004), thirteen Member States of the EU submitted data based on some of the 16 food categories, relevant for the estimation of cadmium intake. The resulting mean intake was around 100 μg/week (range 2.7 - 176 μg/week) or 1.6 μg/kg b.w. for a 60 kg adult. It was noted that none of the Member States reported intake data for all food categories (range 2/16 - 13/16).

Since children have a lower body mass, their body burden per kg body weight will generally be larger than that for adults, but remained below the PTWI.

Table 4. Maximum levels (mg/kg) of cadmium as defined in Commission Regulation (EC) No 466/2001, and reported data from the EU Member States (taken from SCOOP report 2004 (EC, 2004)) (figures above the maximum levels are written in bold).

Product	Max. level	BE	DK	FI	FR	DE	HE	IR	IT	NL	NO	PT	SE	SP	UK
Meat (bovine, sheep, pig and poultry)	**0.05**	0.024	0.002	0.001-0.022	0.04	0.005-0.016	0.004 0.010	0.025-0.045		0.050	0.046		0.002	0.002-0.036	0.008-0.010
Horsemeat	**0.2**	0.041		0.024	0.056				0.075				0.042		
Liver of cattle, sheep, pig and poultry	**0.5**	0.068		0.011-0.034		0.102	0.27	0.081-0.015			0.011		0.028	0.032	0.077
Kidney of cattle, sheep, pig and poultry	**1.0**	0.153		0.162-0.179				0.122-0.22					0.11	0.070	0.11
Muscle fish	**0.05**	<0.001-0.027	0.0034	0.001-0.009	0.007	0.011		0.008-0.004	0.003	0.001-0.049	0.026	0.005	0.017	0.007-0.097	0.013
Muscle fish	**0.1**	<0.001-0.010		0.029			0.057			0.018					
Crustaceans	**0.5**	0.021		0.010	0.087		0.003- 0.004	0.24-**2.54**		0.020-0.10					
Bivalves molluscs	**1.0**	0.403		0.077	0.239	0.116	0.1768- **2.368**	0.166-0.429	0.10	0.017-0.793	**1.125**	0.104			
Cephalopodes (without viscera)	**1.0**	**1.20**					<0.002-0.500		0.002						
Cereals, excl. bran, germ, wheat grain and rice	**0.1**		0.033	0.025-0.056		0.029					0.037	0.027	0.025	0.003-0.015	0.022-0.028
Bran, germ, wheat grain and rice	**0.2**			0.036-0.07					0.035-0.037				0.072		
Soybeans	**0.2**														

Table 4. Continued.

Product	ML	BE	DK	FI	FR	DE	HE	IR	IT	NL	NO	PT	SE	SP	UK
Vegetables and fruits, excl. leafy vegetables, and other products	0.05	<0.005-0.021	0.003-0.018		0.012	0.005-0.052		0.013-**0.20**	0.05-**0.16**	0.01-0.006	0.014	0.043	0.018	0.004-0.017	0.002
Leafy vegetables, fresh herbs, celeriac and all cultivated fungi	0.2	0.045	0.013		0.035			0.086-**0.55**	0.03	0.008-0.042					0.001-0.023
Stem vegetables, root vegetables and potatoes	0.1	0.044	0.010-0.031		0.020			0.086-**0.12**		0.013-0.022		0.038	0.010	0.005-0.061	0.026

CONCLUSIONS AND RECOMMENDATIONS

- Cadmium is a common contaminant of food and feed materials, due to its natural and anthropogenic occurrence in the environment and the resulting levels of cadmium in soils and plants. Elevated concentrations of cadmium in individual feed commodities may occur as a result of regional high cadmium levels in soils, atmospheric deposition of cadmium, and the application of sewage sludge or phosphate fertilizers containing high amounts of cadmium. The present limit for cadmium in complete feedingstuffs is set at 0.5 mg/kg dry matter for all animal species (except pets) and adult ruminants (1 mg/kg).

- In animals, cadmium uptake from feeds varies, depending on the concentrations in feed, the duration of exposure, diet composition, and the nutritional status of the animal.

- Cadmium is toxic to all animal species and accumulates in the kidneys and to a lesser extent in the liver. In most of the domestic animal species, gross clinical symptoms are unlikely to occur if dietary cadmium concentrations remain below 5 mg/kg feed. Pigs have been considered to be the most sensitive species. Significant gross changes (growth retardation) may be expected at concentrations > 4.43 mg/kg dry matter, which is comparable to the commonly recognized tolerance level of 5 mg/kg feeds for all other animal species.

- Whilst pigs are able to tolerate the maximum level set for cadmium in animal feeds, extensive copper supplementation of the diet increases the risk of adverse health effects as under this condition, accumulation of cadmium in liver and kidney is increasing. However, considering the recent limitations in the permissible levels of trace elements in feeds (Council Regulation (EC) 1334/2003)[23] this risk seems to be negligible.

- Accumulation of cadmium in animal tissue is a function of both, dietary concentration and duration of exposure. The short life span of animals like fattening pigs and poultry, both contributing significantly to the human nutrition, minimizes the risk of undesirable cadmium concentrations in edible tissues of these animals. In contrast, regular consumption of offal's such as kidney and liver from aged animals (cattle and horses) and wildlife, will make a more significant contribution to human dietary exposure.

DOCUMENTATION PROVIDED TO EFSA

EC (European Community) 2003. Final draft report from SCOOP task 3.2.11: Assessment of the dietary exposure to arsenic, cadmium, lead and mercury of the population of the EU Member States. Final draft, 05 December 2003.

[23] Commission Regulation (EC) No 1334/2003 has reduced the maximum content of copper in complete feedingstuffs for pigs

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ACKNOWLEDGEMENT

The Scientific Panel on Contaminants in the Food Chain wishes to thank George Bories, Bruce Cottrill, Jean-Pierre Cravedi, Wolfgang Dekant, Johanna Fink-Gremmels, Karl Honikel, Gerard Keck, Josef Leibetseder, Martha Lopez Alonso and Anne-Kathrine Lundebye Haldorsen for the contributions to the draft opinion.