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OPINION

of the French Food Safety Agency on a request for scientific and technical support regarding the migration of cobalt from porcelain oven-dishes intended to come in contact with food

THE DIRECTOR GENERAL

1. CONTEXT OF THE REQUEST

On 31 March 2010, the French Food Safety Agency (AFSSA) received a request from the General Directorate for Competition, Consumer Affairs and Fraud Control (DGCCRF), the Directorate General for Health (DGS) and the Directorate General for Food (DGAL) for scientific and technical support regarding the migration of cobalt from porcelain oven-dishes intended to come in contact with food.

2. BACKGROUND

On 18 February 2010, the German authorities, via the RASFF (Rapid Alert System for Food and Feed) network, issued an alert regarding the migration of cobalt from a porcelain oven-dish imported from China. The analysis performed by the German laboratories revealed migration levels of 0.3 mg/l for cobalt and 1.4 mg/l for lead (analytical reference: DIN EN 1388[1]).

AFSSA was requested to provide scientific and technical support regarding the toxicity of cobalt and the relevance of establishing a maximum migration limit for cobalt in ceramic materials and articles.

3. EXPERT ASSESSMENT METHOD

The request was assessed by studying two scientific Opinions issued by EFSA[2] in 2009[3], documents from ATSDR[4] and RIVM[5], and the RASFF notification.

The collective expert assessment was undertaken by the Scientific Panel on 'Food Contact Materials' (CES MCDA), which met on 4 May 2010.

4. DISCUSSION

Cobalt is a transition metal with two oxidation states (cobalt (II) and cobalt (III)). Cobalt is an essential element as part of vitamin B12 (also called cobalamin), involved in folate and fatty acid metabolism.
It is also found in metal and salt form: sulphate, chloride, oxide, carbonate, etc.

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[1] Materials and articles in contact with foodstuffs, silicate surfaces: –Determination of the release of lead and cadmium from ceramic ware: DIN EN 1388
[2] European Food Safety Authority
[3] Use of cobalt compounds as additives in animal nutrition; Assessment of the safety of cobalt (II) chloride hexahydrate added for nutritional purposes as a source of cobalt in food supplements.
[4] Agency for Toxic Substances and Disease Registry
[5] Dutch National Institute for Public Health and the Environment

Data on oral cobalt exposure via food

According to the Total Diet Study (TDS-1), the estimated average daily intake for the French population is 7.5 µg/day for adults aged 15 years and older and 7.3 µg/day for children aged 3 to 14 years. In adults, daily exposure at the 2.5th and 97.5th percentiles is 3.5 µg and 14 µg respectively. In children, exposure is 3 µg and 15 µg for these same percentiles (INRA/AFSSA, 2004).
Cobalt is ingested as cobalamin via meat products and in inorganic form via plant products.

The EVM[6] gives values of 12 µg/day on average and 19 µg/day at the 95th percentile, i.e. in the same order of magnitude (EVM, 2003).

Data on the toxicity of cobalt after oral exposure

The toxicity of cobalt and its derivative products has been the subject of in-depth investigations (ATSDR, 2004; RIVM, 2001), including a recent EFSA opinion on the use of cobalt compounds as additives in animal nutrition (EFSA, 2009). The majority of the information that is available is related to cobalt (II) compounds. An overview of the toxicity of cobalt is attached to this Opinion.

The IARC[7] has classified cobalt (II) compounds as group 2B carcinogens (possibly carcinogenic to humans).

Data on cobalt in food contact materials

Small quantities of cobalt oxide or sulphate are used in the glass and ceramic industries to neutralise the yellow tint resulting from the presence of iron in glass, pottery and enamels. Larger quantities are used to impart a blue colour to these products (Guidelines of the Council of Europe on metals and alloys used as food contact materials dating from 13 February 2002).

Ceramic materials and articles are regulated in Europe by Directive 84/500/EEC of 20 October 1984, which was transposed into French law by the amended French Order of 7 November 1985 limiting the quantities of lead and cadmium extractable from ceramic articles. This regulation sets migration limits for the metallic elements lead and cadmium, as well as analytical testing methods. Regulatory controls of ceramic articles are subject to an annual DGCCRF plan to test for these two elements.

Currently, there is no specific migration limit (SML) for cobalt in ceramic materials and articles. However, for plastic materials, Directive 2002/72/EC sets a total specific migration limit [SML(T)] of 0.05 mg/kg for cobalt.

Aside from the German authorities' alert and the single analysis result (0.3 mg/l), no cases of cobalt migration from porcelain materials in contact with food have been reported in the literature.

However, the Belgian Scientific Institute of Public Health has undertaken cobalt migration tests in around one hundred ceramic articles[8] on the market (data not published). The results highlighted highly variable amounts of cobalt that regularly exceeded the limit of quantitation (3 µg/l via optical ICP, according to the method stipulated in Directive 84/500/EEC).

5. CONCLUSION

In this context and given cobalt's toxicity, it is appropriate to remain vigilant should new cases of migration be brought to light.

AFSSA considers it would be advisable to perform controls on ceramic recipients in order to better objectify the risk of cobalt migration and thus establish and examine relevant data to define an SML.

With respect to the health-based guidance values applicable to cobalt and in light of the few available studies on oral exposure, AFSSA concludes that the Tolerable Daily Intake could be between 1.6 and 8 µg/kg b.w./day, for threshold toxic effects.

[6] EVM: UK Expert group on vitamins and minerals

[7] International Agency for Research on Cancer

[8] No information is available on the nature and the origin of the analysed articles, or whether there was a protective varnish on their decoration.

However, the genotoxicity data do not allow the possibility of non-threshold toxic effects to be ruled out. Lacking oral carcinogenesis studies, the Threshold of Toxicological Concern could be applied for this type of effect.

Moreover, AFSSA notes that the level of lead migration (1.4 mg/l) is extremely close to the maximum migration limit for storage and cooking recipients (1.5 mg/l).

These are the data that AFSSA is able to provide in response to the request from the DGCCRF, the DGS and the DGAL for scientific and technical support regarding the migration of cobalt from porcelain oven-dishes intended to come in contact with food.

The Director General

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KEYWORDS

Cobalt, porcelain, ceramic, migration.

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ANNEX

Data on the toxicokinetics of cobalt

The gastrointestinal absorption of cobalt in humans varies considerably (by 18 to 97%) according to the dose and the chemical form of cobalt. The bioavailability of cobalt (II) chloride is reported as being higher than other inorganic cobalt compounds.

After oral exposure in animals, cobalt is mainly found in the liver and kidneys. Its half-life in blood is around 24 hours. In humans, irrespective of the route of exposure, the majority of cobalt is eliminated rapidly, mainly in faeces and urine. A small proportion is excreted slowly with a half-life of several years (RIVM, 2001; INRS, 2000; ATSDR, 1992).

Data on the toxic effects of cobalt

Metal cobalt is classified in Annex 6 of Regulation (EC) no. 1272/2008[9] as sensitising and toxic for the environment.

1. Cardiomyopathy and polycythaemia

In the 1960s, cardiomyopathies were reported in people who consumed large amounts of beer containing cobalt sulfate as a foam stabilizer. The estimated average intake of cobalt was reported to range from 0.04 to 0.14 mg of cobalt/kg/day on average for several years (ATSDR, 2004). Cobalt alone causes damage to the heart muscle, whereas the combination of cobalt and alcohol reduces blood flow to the heart, thus leading to anoxia and cardiac damage. In addition, other factors such as a low-protein diet and a history of heart damage related to alcohol consumption have resulted in cardiomyopathies (Lison, 2007).

In animals, high doses of cobalt salts cause polycythaemia (an increase in the total mass of red blood cells) in rats (oral or parenteral administration of cobalt dichloride or dinitrate), heart modifications (increase in heart weight, pericardial effusion and myocardial degeneration) in guinea pigs (oral administration of cobalt sulphate heptahydrate, 20 mg/kg/day for 5 weeks) and functional and morphological thyroid alterations in guinea pigs and rats (cobalt dichloride or oxide, INRS, 2000).

2. Genotoxicity

The genotoxicity of cobalt was recently reviewed (IARC, 2006; WHO, 2006).

In vitro studies

The results of tests performed with soluble cobalt (II) salts (acetate, dichloride and sulphate) have revealed high mutagenic potential in mammalian cells, while the majority of tests performed on bacteria were negative (IARC, 2006).

In vivo studies

Several studies indicate that cobalt salts (dichloride or acetate) can induce genotoxic alterations such as DNA damage, gene mutations, micronuclei formation and chromosomal aberrations in animals after oral or parenteral exposure.

Male mice administered a single dose of cobalt (in the form of cobalt dichloride) at 0; 4.96; 9.92 or 19.8 mg/kg body weight exhibited a dose-response increase in percentages of chromosomal breaks and aberrations in bone marrow cells (EFSA, 2009).

[9] Regulation (EC) no. 1272/2008 of the European Parliament and Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) no. 1907/2006.

With respect to the data available in the literature, the RIVM document suggests that it can be concluded that most *in vitro* mutagenicity tests on bacteria for cobalt and its compounds are negative. Positive results have been observed in DNA damage studies in mammalian cells (RIVM, 2001).

In its 2006 evaluation, the IARC concluded that: "The results of genotoxicity assays with cobalt salts demonstrate clearly their mutagenic potential". On the basis of sufficient animal data on somatic cells, the European Commission has classified cobalt (II) chloride hexahydrate as mutagenic (Mutagen Category 3, R68).

Some cobalt compounds (dichloride, sulphate, diacetate, nitrate, carbonate) have been classified by the European Union as of concern to humans due to their possible mutagenic effects (harmonised classification, Annex 6 of Regulation (EC) no. 1272/2008).

3. Carcinogenicity

There are no carcinogenicity data for cobalt salts after oral exposure. The classifications established by the IARC are essentially based on inhalation exposure, as the available data come from the follow-up of workers employed in cobalt production plants. Various studies which followedup workers in metal production plants have provided evidence of an increased lung cancer risk related to exposure to hard-metal dust containing cobalt and tungsten carbide (Lison, 2007; EFSA, 2009).

The IARC therefore classified cobalt and its derivative products (metal alloys, cobalt (II) and (III) compounds) in group 2B (possibly carcinogenic to humans) in 1991. The overall evaluation undertaken by the IARC in 2006 concluded that cobalt metal (without tungsten carbide), cobalt sulphate and soluble cobalt (II) salts are also possibly carcinogenic to humans whereas cobalt metal with tungsten carbide is classified in group 2A (probably carcinogenic to humans).

Some cobalt compounds (dichloride, sulphate, diacetate, nitrate, carbonate) have been classified by the European Union as presumed human carcinogens when inhaled (harmonised classification, Annex 6 of Regulation (EC) no. 1272/2008).

4. Reproductive toxicity

No studies have been recorded on the effects of oral cobalt exposure on human reproduction (INRS, 2000).

Testicular degeneration and atrophy were reported in rats exposed to doses of 13.3 to 58.9 mg of cobalt/kg/day in the form of cobalt chloride in feed or drinking water for 2 to 3 months, and in mice exposed to 43.4 mg of cobalt/kg/day in the form of cobalt chloride in drinking water for 13 weeks (ATSDR, 2004).
Cobalt dichloride (rats, oral exposure, 5.4 or 21.8 mg/kg/day from the 14th day of gestation to the 21st day of lactation) causes maternal toxicity, as well as retarded growth and/or a lower survival rate in offspring. On the other hand, higher doses (up to 100 mg/kg/day) administered from the 6th to 15th day of gestation are not foetotoxic or teratogenic in spite of clear maternal toxicity. Likewise, no effects on foetal growth or fatality have been observed in mice (81.7 mg/kg/day from the 8th to 12th day of gestation, INRS, 2000).

Some cobalt compounds (dichloride, sulphate, diacetate, nitrate, carbonate) have been classified by the European Union as presumed toxic to human fertility (harmonised classification, Annex 6 of Regulation (EC) no. 1272/2008).

5. Effects on the immune system

Cobalt appears to function as a hapten[10], like nickel, which causes antibodies against cobalt-protein complexes to develop(Thierse *et al.,* 2005). The most common hypersensitivity reaction to cobalt is allergic contact dermatitis (EFSA, 2009).

6. Effects on the thyroid

Altered thyroid function associated with cardiomyopathy occurred in humans consuming large quantities of beer containing cobalt as a foam stabilizer (ATSDR, 2004; EFSA, 2009).

[10] Hapten: small antigenic molecule capable of being recognised by the immune system but not immunogenic.

Cobalt and Health-based guidance values

Three health-based guidance values are currently available for cobalt compounds by ingestion.

- Health-based guidance value **of the ATSDR, adopted by EFSA**

The ATSDR considers that there are not sufficient studies to date on chronic oral exposure to cobalt or its compounds.
The cases of human poisoning with cobalt sulphate have not been used to establish a chronic MRL (Minimal Risk Level) due to the concomitant alcohol levels.
An intermediate-duration MRL of **10 µg of cobalt/kg/day** was derived from a lowest observed adverse effect level (LOAEL) of 1 mg/kg/day of cobalt administered orally (in the form of cobalt chloride) to volunteers for 22 days (Davis and Fields, 1958). Polycythaemia was considered to be the most sensitive parameter. An uncertainty factor of 100 was applied: 10 for human variability, and 10 for use of a LOAEL (ATSDR, 2004).

The MRL was confirmed by an 8-week study in rats administered cobalt chloride which established a NOAEL (no observed adverse effect level) of 600 µg of cobalt/kg/day (LOAEL of 1 mg/kg/day) (Stanley *et al*., 1947).

EFSA adopted the ATSDR value and established that a **daily oral intake of 600 µg of cobalt** appears to be a minimum risk level for humans that would protect from the known threshold-related adverse effects on the basis of the subacute MRL of 10 µg of cobalt/kg/day for a 60 kg individual (EFSA, 2009).

AFSSA considers that an uncertainty factor could however have been applied to the ATSDR MRL value to take into account subacute to chronic exposure extrapolation. The value used in the REACh guidance documents for this extrapolation is 6, which brings the daily oral intake to 100 µg of cobalt (1.6 µg/kg/day).

Furthermore, AFSSA notes that the use of the rat study by Stanley *et al.* (1947) with an inter-species factor of 4 (rats to humans) and an intra-species factor of 10 leads to a final value of 16 µg of cobalt/kg/day, which is close to the adopted MRL value. An additional safety factor of at least 2 should however be applied to take into account the extrapolation from subchronic exposure (90 days) to chronic exposure (lifetime). This leads to a final value smaller than 8 µg of cobalt/kg/day (the rat study lasted for 56 days).

- Health-based guidance value **of the RIVM**

In 1991, a TDI of **1.4 µg of cobalt/kg/day** was presented in a report from RIVM.
The Tolerable Daily Intake (TDI) has been maintained on the basis of an LOAEL of 40 µg/kg/day for cardiomyopathy after intermediate oral exposure in beer drinkers (Morin *et al.* 1971). As the role of alcohol cannot be excluded in the observed effects, the RIVM considers that it can be expected that the LOAEL for the general population will be higher and that an uncertainty factor of 3 for inter-individual variability is to be used. The uncertainty factor used is therefore 30 (3 for intra-human variability and 10 for extrapolation to a NOAEL). Under these conditions, the RIVM considers that the TDI that was established in 1991 can be maintained (RIVM, 2001).

- Health-based guidance value **of the EVM**

The EVM proposes a guidance level on the basis of adverse effects on spermatogenesis (cobalt chloride in mice for 13 weeks). A LOAEL of 23 mg of cobalt/kg/day was established (Pedigo *et al*., 1988). An uncertainty factor of 1000 was adopted (10 for inter-species variation, 10 for inter-individual variation and 10 for LOAEL to NOAEL extrapolation). Therefore, an intake of **23 µg of cobalt/kg/day** would not be expected to result in any adverse effects**.**

AFSSA considers that according to the REACh technical documents, the LOAEL-to-NOAEL extrapolation factor should be 3 (or 10), the inter-species factor 7 (mice), the subchronic-to-chronic exposure extrapolation factor 2 and the intra-species factor 10, which leads to a total factor of 1400 to 420. The guideline value would then be between 16.4 and 54.8 µg of cobalt/kg/day, or 1 and 3.3 mg of cobalt/day.