

Duke University Medical Center
Department of Community & Family Medicine
Division of Occupational & Environmental Medicine
Box 3834
Durham, NC 27710
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Tel: 919-286-5744
FAX: 919-286-5647

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, NE
Mail Stop E-29
Atlanta, GA 30333

Re: Comments concerning your Draft Toxicology Profile for Cobalt

Dear Sirs:

I am an occupational physician and internist and head the toxicology program within our Division of Occupational and Environmental Medicine. I have reviewed the sections on risks associated with the ingestion of cobalt, including an MRL risk assessment for the same. My comments are limited to the basis for this risk assessment and recommendations for alternate approaches to determining an MRL for oral exposure to cobalt. ATSDR made the incorrect presumption that exposure to cobalt gives a risk of developing polycythemia vera and ignored more sensitive endpoints, hypothyroidism and myocardopathy, for which there is chronic exposure data in humans, as alternates for this risk assessment. Utilization of these latter endpoints would give a more conservative MRL.

Proposed ATSDR MRL Risk Assessment based on Polycythemia

ATSDR utilizes an acute exposure study of cobalt ingestion in humans and associated polycythemia as an end point for the intermediate MRL risk assessment for oral exposure to cobalt. The choice of this end point is justified because “at higher erythrocyte levels, the condition may progress to a diagnosis of polycythemia vera, which could result in clot formation and blockage of small blood vessels,...[and] may result in eventual failure of bone marrow.” This approach is weak both because of an invalid risk assumption and because lower exposure, long term human studies were not considered.

Cobalt exposure causes a secondary polycythemia because of depression of oxidative phosphorylation and resultant tissue hypoxemia (Yastrebov, 1965). The resultant hypoxemia stimulates erythropoietin production (Smith & Fisher, 1971) with resultant bone marrow stimulation of red blood cell production. This secondary polycythemia is very much like that seen with hypoxemia secondary to chronic lung disease, the latter being the major cause of secondary polycythemia. This type of polycythemia is not

associated with elevations of platelet or white blood cell counts, morphologic changes of megakaryocytes, myelofibrosis of bone marrow with associated anemia or risk of leukemia. In fact, it was used to stimulate red cell production in patients with chronic anemia secondary to such disorders as chronic kidney disease, aplastic anemia or sickle cell disease prior to the development of a commercial form of erythropoietin.

Polycythemia vera is a myeloproliferative disease that is secondary to mutations in bone marrow stem cells, clonal expansion of these transformed hemopoietic stem cells and resultant overproduction of red blood cells, white blood cells and platelets (Pearson et al., 2000). Unlike secondary polycythemia, complications include increased platelet counts with associated thromboses, myelofibrosis of the bone marrow with associated anemia, and leukemia. (Najean et al, 1996; Thiele and Kvasnicka 2001). Diagnostic criteria for polycythemia vera also differ from those for secondary polycythemia. Where both are associated with increased red blood cell production, erythropoietin levels in secondary polycythemia are elevated while they are low in polycythemia vera. Spleen enlargement and increases in the numbers of circulating white blood cells and platelets can be found in polycythemia vera but are not seen as part of secondary polycythemia (Pearson, 2001). Further, bone marrow in polycythemia vera has distinct findings including hypercellularity of all lines, hyperplasia and giant megakaryocytes where only increased cellularity of the erythroid line is seen in secondary polycythemia (Michiels, 1997; Thiele, et al, 2001). In fact, the diagnostic criteria for polycythemia vera versus secondary polycythemia are mutually exclusive (Pearson & Messinezy, 1996; Vicari et al, 1998).

Secondary polycythemia is, however, a marker for the toxicity of cobalt, being found in association with diseases, such as hypothyroidism or cardiomyopathy, that are associated with risks of death or serious ill health. There are several clinical studies for individuals chronically exposed to cobalt which have looked at polycythemia as an end point. The most sensitive are summarized in Table I. Of particular import is the finding of polycythemia in populations of alcoholics who were drinking beer amended with soluble cobalt salts to preserve the foam "head". Within 2 months of the introduction of this process, alcoholics drinking large quantities of this beer developed a syndrome of cardiomyopathy, hypothyroidism and polycythemia. Kersteloet et al. (1968) described this syndrome in Belgium drinkers of cobalt-amended beer who had deficient diets but did not find it in alcoholics drinking the same beer who did not have deficiencies. In a group of well-nourished alcoholics drinking 16 glasses of beer containing 1 ppm (0.05 mg Co/kg bw/day, assuming 70 kg body weight), no polycythemia was found. Aminoacids and proteins bind to cobalt and can decrease its absorption: this may explain why one population appeared to be more sensitive to the hematopoietic effects than the other (Wiberg et al, 1969).

Cardiomyopathy

Cardiomyopathy with altered cardiac pathology and/or pericardial effusions has been identified in a number of studies, summarized in Table II. This disease was identified within 2 months of exposure to cobalt-amended beer among alcoholic populations drinking this beer. Cobalt has been used for treating individuals with chronic anemia. One such treated infant developed both a goiter and a pericardial effusion after 3 months of treatment (Little

& Sunico, '58). In well-nourished populations, whether or not they are alcoholic, exposure to low levels of cobalt has not been associated with a risk of cardiomyopathy or pericardial effusion. Kersteloet et al (1968) did not find any evidence of cardiac disease in his healthy population of beer-drinkers exposed to 0.05 mg Co/kg bw/d. Alcoholics may be deficient in thiamine, a co-factor that prevents oxidative metabolism at the same site in the citric acid cycle as affected by cobalt (Alexander, 1972). Alcoholics with thiamine deficiency have been found among populations with cobalt myocardopathy (Morin et al, 1971).

Goiter and hypothyroidism

Cobalt prevents uptake of iodine into the hormone thyroxine through its inhibition of tyrosine iodinase (Alexander, 1972). This results in a drop in circulating thyroxine levels which may lead to clinical hypothyroidism. Because of the low thyroxine levels, the excretion of thyroid stimulating hormone is increased with resultant thyroid hormone hyperplasia (goiter). This stimulation can occur in populations that are not sensitive to the cardiotoxic effects of cobalt. Cobalt exposures that increase the risk of cardiomyopathy also cause thyroid pathology in those with heart disease (Morin & Daniel, 1967; Bonenfant et al 1969; Table III). Estimated cobalt exposure to this population was 5-10 mg/day (0.07-0.14 mg Co/kg bw/day). Kersteloet et al, 1968, examined a beer-drinking population chronically exposed to cobalt and found no evidence of goiters on a physical examination. The average cobalt exposure to this population was 0.05 mg Co/kg bw/day. Shorter term exposures to cobalt have occurred in children and adults to levels as high as 1.8 mg/kg bw/day without noticeable effects on the thyroid. In one of these populations, thyroid suppression occurred at a daily dose of 2.7 mg Co/kg bw (Table III).

Recommendation

ATSDR's proposed MRL is based on a mechanism without pathophysiological basis and using an acute study where individuals were exposed to high levels of cobalt, well above the minimum levels associated with hematopoietic effects. Although one endpoint can be used for determining a minimum risk level for the oral exposure to cobalt, a series of endpoints, all occurring at similar cobalt exposures and in similarly exposed populations, will give a stronger and more conservative assessment of risk. Cobalt inhibits a number of enzymes which results in a number of effects including polycythemia associated with tissue hypoxemia (NOEL 0.05 mg Co/kg-bw/day), goiter and hypothyroidism (NOEL 0.05 mg Co/kg-bw/day) and cardiac toxicity in populations with inadequate intakes of protein, thiamine and other nutrients that might make them more sensitive to the toxic effects of cobalt (LOEL 0.06 mg Co/kg-bw/day). With adequate nutrition, even in alcoholic beer drinkers consuming cobalt-tainted beer, no cardiotoxic effects have been seen (NOEL 0.05 mg Co/kg-bw/day).

Cobalt has been used for treating children and infants, including premature infants, who are anemic. Exposures have been sufficient to cause goiters and hypothyroidism within months of exposure. The lowest observed effect level for thyroid effects in children is 0.13 mg Co/kg-bw/day yet populations of similarly-aged children have been able to tolerate up to 1.8 mg Co/kg-bw/day without thyroid effects. Cobalt was used in combination with iron to treat anemic children. Cobalt is absorbed by the same pathway as iron and iron deficiency can double the absorption of cobalt (Alexander, 1972).

Children with iron deficiency would be expected to have a greater absorption of cobalt and have increased sensitivity to its toxic effects similar to exposed adults who appear to be sensitive because of nutritional deficiencies. An MRL for the oral exposure that is set to protect sensitive adult populations would likely protect sensitive populations of nutritionally deficient children as well.

Respectfully submitted,

Woodhall Stopford, MD, MSPH

Table I: Cobalt and Polycythemia in Man

<u>Dose</u> (mg/kg/d)	<u>number</u> <u>Subjects</u>	<u>Duration</u>	<u>Outcome</u>	<u>Assessment</u>	<u>Reference</u>
0.06	18 Belgium beer drinkers		polycythemia	LOEL	Kersteloot et al '68
0.05	12 brewery workers		No polycythemia	NOEL	Kersteloot et al '68
0.13	1 12 y.o.	3 mos	polycythemia	LOEL	Sederholm et al '68
0.07-0.14	50 Quebec beer drinkers	2+mos	No polycythemia	NOEL	Morin et al. '71

Table II: Cobalt and Myocardopathy in Man

<u>Dose</u> (mg/kg/d)	<u>number</u> <u>Subjects</u>	<u>Duration</u>	<u>Outcome</u>	<u>Assessment</u>	<u>Reference</u>
0.06-0.07	64 Omaha beer drinkers	2+ mos	47% mortality	LOEL	Sullivan et al '69
0.05	12 brewery workers	2+yrs	No heart disease	NOEL	Kersteloot et al '68
0.06	18 Belgium beer drinkers	1+ yrs	myocardopathy, no deaths	LOEL	Kersteloot et al '68
0.07-0.14	50 Quebec beer drinkers	2+mos	40% mortality	LOEL	Morin & Daniel '67
0.14	1 adult with aplastic anemia	4 mos	heart failure	LOEL	Kersteloot et al '68
0.08-1.0	adults rx for hypertension	up to 8 yrs	No heart disease	NOEL	Jaquet '49

Table III: Cobalt and Thyroid Disease in Man

<u>Dose</u> (mg/kg/d)	<u>number</u> <u>Subjects</u>	<u>Duration</u>	<u>Outcome</u>	<u>Assessment</u>	<u>Reference</u>
1	12 adults	12 wks	depressed I131 uptake	LOEL	Roche et al. '56
1.3-1.8	5 children	2-7 mos	goiter, hypothyroidism	LOEL	Kriss et al. '55
1.8	15 children	10 wks	thyroid function normal	NOEL	Jaimet & Thode '55
2.7	2 children	10 wks	depressed I131 uptake	LOEL	Jaimet & Thode '55
0.4-0.6	78 pregnant women	90 days	No goiter	NOEL	Holly '56
0.3-11	3 infants	2-10 mos	goiter, hypothyroidism	LOEL	Chamberlain '61
0.07-0.14	20 quebec beer drinkers		cobalt goiter/thyroid disease	LOEL	Morin & Daniel '67; Bo
0.16-0.32	12 anephric adults	12-47 wks	1/12 with hypothyroidism	LOEL	Duckham & Lee '76
0.9-1.4	4 15 mos-7 yrs old	6-7 mos	goiter, hypothyroidism	LOEL	Gross et al '55
0.13	1 12 y.o.	3 mos	goiter, hypothyroidism	LOEL	Sederholm et al '68
0.3	1 3 y.o.	8 mos	goiter	LOEL	Washburn & Kaplan '68
0.05	12 brewery workers	2+yrs	No goiter	NOEL	Kersteloot et al '68

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