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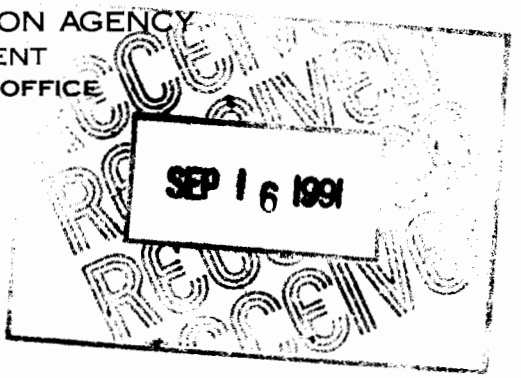

Dr. Bruce Swanton
New Mexico Environmental Department
Hazardous and Radioactive Materials Bureau
1190 St. Francis Drive
Santa Fe, NM 87502

RE: Oral Slope Factors and Reference Doses for Cobalt, Copper and Chrysene (Kirtland Air Force Base/ New Mexico)

Dear Dr. Swanton:

This memo is in response to a request from Mike Silva of GeoScience Consultants for oral slope factors and reference doses for copper, cobalt and chrysene. Enclosed please find the following:

Enclosure I: Risk Assessment Issue Paper for the Interim Oral Slope Factor and Reference Dose for Copper

Enclosure II: Risk Assessment Issue Paper for the Interim Oral Slope Factor and Reference Dose for Cobalt

Enclosure III: Risk Assessment Issue Paper for the Interim Oral Slope Factor and Reference Dose for Chrysene

Please feel free to contact ECAO at (513) 569-7300 if we can be of further assistance.

Respectfully,

Cindy Sonich-Mullin

Cindy Sonich-Mullin, Chief
Chemical Mixtures Assessment Branch

Enclosures

cc: J. Dinan (OS-230)
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M. Silva (GeoScience Cons.)
S. Weldert (ECAO-Cin)

Enclosure I

Risk Assessment Issue Paper for: Oral Slope Factor and Reference Dose for Copper

Reference Dose

The emetic properties of copper have been known for some time. There are several reports of gastrointestinal disturbances (e.g. vomiting, diarrhea, abdominal pain) in individuals consuming beverages contaminated with copper (ATSDR 1989). The lowest level that elicit a response was approximately 5 mg (0.07 mg/kg/day). Extensive hepatic centrilobular necrosis has also been observed in individuals intentionally consuming a single, large dose of copper sulfate (Chuttani et al. 1965). Two reports of health effects in humans exposed repeatedly to copper were discussed in the ATSDR profile (ATSDR 1989). The first report involved a family that drank copper contaminated water in the morning for approximately 1.5 years. Recurrent and acute episodes of nausea, vomiting and abdominal pain were reported. Samples of the morning water contained 7.8 mg/L copper (Spitalny et al. 1984). The second report involved 2 infant siblings exhibiting liver damage (hepatosplenomegaly, cirrhosis). The infants drank contaminated tap water (2-3 mg Cu/L) for $\leq$ 9 months (Mueller-Hoecker et al. 1988). It should be noted that children under 1 year of age are unusually susceptible to the toxicity of copper because homeostatic mechanisms for clearing copper from the body and regulating its gastrointestinal absorption have not fully developed at this age. Because both of these reports have a small sample size and actual water intakes were not reported, neither study is adequate for the derivation of an oral RfD.

Numerous animal subchronic studies which demonstrate the toxicity of copper in rats and pigs were reviewed by ATSDR (1989). The liver appears to be a primary target organ for copper toxicity. Hepatic centrilobular necrosis followed by regeneration was observed in rats administered $\geq$ 100 mg/kg/day. Alterations in serum enzymes (e.g. SGOT) which may be indicative of liver damage have been observed at dietary concentrations of approximately 40 mg/kg/day. A number of studies have demonstrated the development of tolerance to copper toxicity in rats and pigs (ATSDR 1989). It is not known if humans would also develop tolerance to copper toxicity, therefore it is not clear whether rats and pigs may serve as a good model for human copper toxicity.

In conclusion, in order to protect against the adverse health effects associated with copper deficiency the RfD for copper should be at least 2×10^{-2} to 4×10^{-2} mg/kg/day, a range considered as "safe and adequate" for copper intakes for adults

(NAS, 1989). FAO/WHO expert committee on food additives concluded that a copper intake (from dietary sources) as high as 0.5 mg/kg/day would not result in adverse health effects (FAO/WHO 1971). However, individuals drinking beverages contaminated with approximately 7×10^{-2} mg/kg/day exhibited signs of gastrointestinal disturbances. Thus, an interim RfD for copper should fall between 4×10^{-2} mg/kg/day and 7×10^{-2} mg/kg/day.

References:

ATSDR. 1989. Toxicological Profile for Copper. Agency for Toxic Substances and Disease Registry, U.S. Public Health Service. Public Comment Draft.

Chuttani, H.K., P.S. Gupta, S. Sharma, et al. 1965. Acute copper sulphate poisoning. Ann. Intern. Med. 82: 266-227. Cited in ATSDR, 1989.

Mueller-Hoecker, J., U. Meyer, B. Wiebecke, et al. 1988. Copper storage disease of the liver and chronic dietary copper intoxication in two further German infants mimicking Indian childhood cirrhosis. Pathol. Res. Pract. 183: 39-45. Cited in ATSDR, 1989.

NAS 1989. Recommended Dietary Allowances, 10th edition. National Academy of Science, National Research Council, Food and Nutrition Board. Washington, D.C.: National Academy Press.

Spitalny, K.C., J. Brondum, R.L. Vogt, et al. 1984. Drinking-water induced intoxication in a Vermont family. Pediatrics 74: 1103-1106.

Slope Factor

Copper is verified as a class D carcinogen (U.S. EPA, 1991), thus data are inadequate for a quantitative cancer risk estimate.

Reference:

U.S. EPA. 1991. Integrated Risk Information System (IRIS). Online. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

Enclosure II

Risk Assessment Issue Paper for: Oral Slope Factor and Reference Dose for Cobalt

Reference Dose

We are providing below the documentation and derivation of an interim oral RfD of 1E-5 mg/kg/day for cobalt. The confidence for the interim oral RfD is low because:

1) No-observed-adverse-effect-levels (NOAELs) for sensitization (the basis of RfD) were not identified.

2) People sensitized by nickel (~2% of men and ~10% of women) may have and allergic reaction following cobalt exposure due to the interrelationships between cobalt and nickel sensitization.

Please note that the number calculated in this issue paper is an interim value and ECAO-Cin is in the process of seeking additional review and comment of this assessment.

The data regarding the toxicity of cobalt is extensive following both oral and inhalation exposure. The primary target organs of cobalt toxicity are the heart and hematopoietic system following oral exposure. Cobalt has also been found to be a sensitizer in humans.

Most of the oral data in humans deals with the cardiomyopathy seen in people who drank large quantities of beer containing cobalt chloride (used to stabilize the foam) (Alexander, 1969, 1972; Morin et al., 1971). The people ingested 0.04-0.14 mg cobalt/kg/day (approximately 8-30 pints of beer daily) over a period of years (Alexander, 1969, 1972; Morin et al., 1971). The cardiomyopathy in the beer-drinkers, termed "beer-cobalt cardiomyopathy", was fatal to 43% of the subjects within several years, with approximately 18% of these deaths occurring within the first several days. The beer-cobalt cardiomyopathy appeared to be similar to alcoholic cardiomyopathy and beriberi, but the onset of the beer-cobalt cardiomyopathy was much more abrupt. The practice of adding cobalt to beer to stabilize the foam has been discontinued.

Cobalt has been found to stimulate the production of red blood cells in humans and, therefore, has been used as a treatment for anemia. Polycythemia was found in anemic patients following oral treatment with 0.16-1.0 mg cobalt/kg daily as cobalt chloride for a period of 3-32 weeks (Davis and Fields, 1958; Taylor et al., 1977). An increase in hematocrit and hemoglobin levels was not observed, however, in pregnant women

treated with 0.5-0.6 mg cobalt/kg/day for 90 days in an attempt to alleviate the anemia often found during pregnancy.

Three studies were located examining the developmental effects of orally administered cobalt (given as cobalt chloride) in rodents (Domingo et al., 1985; Paternain et al., 1988; Seidenberg, 1986). Domingo et al. (1985) treated pregnant female rats to 5.4 to 21.8 mg cobalt/kg/day from gestation day 14 through lactation day 21. Fetal effects included stunted growth of the pups at 5.4 mg/kg/day and decreased survival at 21.8 mg/kg/day. These effects occurred at levels that were maternally toxic (authors did not specify the effects), therefore, the effects may be a result of maternal toxicity and not cobalt treatment. No teratogenic effects were reported.

No significant effects on fetal growth or survival were found in rats exposed to 6.2 to 24.8 mg cobalt/kg/day during gestation days 6-15 (Paternain et al., 1988), although a nonsignificant increase in the incidence of stunted fetuses was found in the animals treated with 12.4 or 24.8 mg cobalt/kg/day. Maternal effects, however, including reduced body weight and food consumption and altered hematological parameters, were reported. No fetal effects were reported in mice exposed to 81.7 mg cobalt/kg/day during gestation days 8-12 (Seidenberg, 1986), but a significant decrease in maternal weight was found.

Several studies reported testicular degeneration and atrophy in rats exposed to 5.7 to 30.2 mg cobalt/kg/day as cobalt chloride for 2-3 months in the diet or in the drinking water (Corrier et al., 1985; Domingo et al., 1984; Mollenhauer et al., 1985; Nation et al., 1983; Pedigo et al., 1988).

One sensitization study was located in which cobalt-exposed workers were challenged orally with cobalt. In this study, several patients with eczema of the hands were challenged orally with 1 mg cobalt (as cobalt sulfate) in tablet form once per week for 3 weeks and 28/47 patients had a flare of dermatitis following the oral challenge (Veien et al., 1987). Forty-seven patients had positive patch tests to cobalt (13 to cobalt alone and 34 to nickel and cobalt) and 7 of the 13 patients that patch tested positive to cobalt reacted to the oral challenge. Using both the oral challenge and dermal patch tests, it was determined that the cobalt allergy was systemically induced. The exposure level associated with sensitization to cobalt was not established. The oral dose of 1 mg cobalt that resulted in the flare up of the dermatitis can be expressed as 0.014 mg cobalt/kg body weight (1 mg x 1/70 kg body weight). Application of an uncertainty factor of 1000 (10 for the use of a LOAEL, 10 for the use of an acute study and 10 to protect sensitive individuals) to the LOAEL of 0.014 mg cobalt/kg/day for sensitization yields an interim oral RfD of 1×10^{-5} mg cobalt/kg/day.

Confidence in the interim oral RfD is low. NOAELs were not identified for sensitization in humans, therefore, it is impossible to certify that the RfD would be protective for sensitive individuals. Also, because interrelationships have been found to exist between cobalt and nickel sensitization, people sensitized by nickel may have an allergic reaction following cobalt exposure. This results in even greater uncertainty in the RfD.

References:

Alexander, C.S. 1969. Cobalt and the heart. Ann. Int. Med. 70:411-413.

Alexander, C.S. 1972. Cobalt-beer cardiomyopathy: A clinical and pathologic study of twenty-eight cases. Am. J. Med. 53:395-417.

Bencko, V., Wagner, V., Wagnerova, M., et al. 1983. Immuno-biochemical findings in groups of individuals occupationally and non-occupationally exposed to emissions [sic] containing nickel and cobalt. J. Hyg. Epidemiol. Microbiol. Immunol. 27:387-394.

Corrier, D.E., Mollenhauer, H.H., Clark, D.E., et al. 1985. Testicular degeneration and necrosis induced by dietary cobalt. Vet. Pathol. 22:610-616.

Davis, J.E., Fields, J.P. 1958. Experimental production of polycythemia in humans by administration of cobalt chloride. Proc. Soc. Exp. Biol. Med. 37:96-99.

Davison, A.G., Haslam, P.L., Corrin, B., et al. 1983. Interstitial lung disease and asthma in hard-metal workers: Bronchoalveolar lavage, ultrastructural and analytical findings and results of bronchial provocation tests. Thorax 38:119-128.

Demedts, M., Gheysens, B., Nagels, J., et al. 1984. Cobalt lung in diamond polishers. Am. Rev. Respir. Dis. 130:130-135.

Domingo, J.L., Llobet, J.M., Bernat, R. 1984. A study of the effects of cobalt administered orally to rats. Arch. Pharmacol. Toxicol. 10:13-20.

Domingo, J.L., Paternain, J.L., Llobet, J.M., et al. 1985. Effects of cobalt on postnatal development and late gestation in rats upon oral administration. Rev. Esp. Physiol. 41:293-298.

Holly, R.G. 1955. Studies on iron and cobalt metabolism. J. Am. Med. Assoc. 158:1349-1352.

Kusaka, Y., Yokoyama, K., Sera, Y., et al. 1986a. Respiratory disease in hard metal workers: An occupational hygiene study in

a factory. Br. J. Ind. Med. 43:474-485.

Kusaka, Y., Ishikawa, Y., Shirakawa, T., et al. 1986b. Effect of hard metal dust on ventilatory function. Br. J. Ind. Med. 43:486-489.

Lammintausta, K., Pitkanen, O.P., Kalimo, K., et al. 1985. Interrelationship of nickel and cobalt contact sensitization. Cont. Dermat. 13:148-152.

Mollenhauer, H.H., Corrier, D.E., Clarke, D.E., et al. 1985. Effects of dietary cobalt on testicular structure. Virchows Arch. B. Cel. Pathol. Incl. Mol. Pathol. 49:241-248.

Morin, Y., Tetu, A., Mercier, G. 1971. Cobalt cardiomyopathy: Clinical aspects. Br. Heart J. 33:175-178.

NTP (National Toxicology Program). 1990. Subchronic Inhalation Studies of Cobalt Sulfate Heptahydrate in F344/N Rats and B6C3F1 mice. Post-Peer Review Technical Report in Progress, NTP TR No. 5.

Nation, J.R., Bourgeois, A.E., Clark, D.E., et al. 1983. The effects of chronic cobalt exposure on behavior and metallothionein levels in the adult rat. Neurobehav. Toxicol. Teratol. 5:9-15.

Paternain, J.L., Domingo, J.L., Corbella, J. 1988. Developmental toxicity of cobalt in the rat. J. Toxicol. Environ. Health 24:193-200.

Pedigo, N.G., George, W.J., Anderson, M.B. 1988. Effects of acute and chronic exposure to cobalt on male reproduction in mice. Repro. Toxicol. 2:45-53.

Raffn, E., Mikkelsen, S., Altman, D.G., et al. 1988. Health effects due to occupational exposure to cobalt blue dye among plate painters in a porcelain factory in Denmark. Scand. J. Work Environ. Health 14:378-384.

Rystedt, I., Fischer, T. 1983. Relationship between nickel and cobalt sensitization in hard metal workers. Cont. Dermat. 9:195-200.

Seidenberg, J.M., Anderson, D,G., Becker, R.A. 1986. Validation of an in vivo developmental toxicity screen in the mouse. Teratogen. Carcinogen. Mutat. 6:361-374.

Shirakawa, T., Kusaka, Y., Fujimura, N., et al. 1988. The existence of specific antibodies to cobalt in hard metal asthma. Clin. Allergy 18:451-460.

Shirakawa, T., Kusaka, Y., Fujimura, N., et al. 1989. Occupational asthma from cobalt sensitivity in workers exposed to hard metal dust. Chest 95:29-37.

Sprince, N.L., Oliver, L.C., Eisen, E.A., et al. 1988. Cobalt exposure and lung disease in tungsten carbide production: A cross-sectional study of current workers. Am. Rev. Respir. Dis. 138:1220-1226.

Taylor, A., Marks, V., Shabaan, A.A., et al. 1977. Cobalt induced lipaemia and erythropoiesis. Dev. Toxicol. Environ. 1:105-108.

Veien, N.K., Hattel, T., Justesen, O., et al. 1987. Oral challenge with nickel and cobalt in patients with positive patch tests to nickel and/or cobalt. Acta. Derm. Venereol. 67:321-325.

Oral Slope Factor

Stable cobalt is a class D carcinogen, thus data are inadequate for calculation of a quantitative cancer estimate (U.S. EPA, 1990). Radioactive cobalt isotopes are class A carcinogens and an interim oral slope factor of 9.7E-6 fatalities/μCi ingested has been calculated for ^{60}Cobalt (U.S. EPA, 1990).

Reference:

U.S. EPA. 1990. Health Effects Assessment for Cobalt. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response. Draft.

Enclosure III

Risk Assessment Issue Paper for:
Oral Slope Factor and Reference Dose for Chrysene

Toxicity Information

I. RfDs/RfCs

Oral

Only 6 PAHs have interim oral RfDs. Table 1 lists the chemicals with oral RfDs along with the critical study, species, critical effect and reference dose. For the 5 chemicals that have been verified, the date of verification is listed, and the RfDs are available on IRIS.

Inhalation
Inhalation RfCs have not been calculated for any of the PAHs.

Carcinogenic Assessment

I. Background

The Office of Emergency and Remedial Response (OERR) is working on a draft approach for risk assessment of PAHs at Superfund sites. ECAO-Cin has been involved in the development of an ODW document for PAHs and is currently working on a Multimedia document for PAHs, both of which discuss toxicity equivalency factors for PAHs. There is presently no Agency position on this issue. It is likely that benzo[a]pyrene will serve as the reference point for TEF approaches to PAH risk assessments. The majority of PAH likely to be found in the environment appear to be less potent than benzo[a]pyrene. There are data, however, to indicate tht methylated PAH and those containing oxygen and nitrogen may be more potent than benzo[a]pyrene.

II. Slope Factors and Interim Approach

Benzo[a]pyrene has been classified as a B2, probable human carcinogen, however, there are no slope factors on IRIS. U.S. EPA (1980, 1984) derived an upper-bound oral slope factor of 11.5 per (mg/kg)/day using a linearized multistage procedure and the data of Neal and Rigdon (1967). U.S. EPA (1984) derived an upper-bound inhalation slope factor of 6.1 per (mg/kg)/day based on the data of Thyssen et al. (1981). These values could be

adopted as interim values for the risk assessment of Superfund Sites. While slope factors for other PAH compounds having a B2 classification are not available, OHEA suggests that benzo[a]pyrene estimates may be useful.

Carcinogen classifications for several PAHs that have been verified are listed below:

Acenaphthylene - D
Anthracene - D
Benz[a]anthracene - B2
Benzo[b]fluoranthene - B2
Benzo[k]fluoranthene - B2
Benzo[g,h,i]perylene - D
Chrysene - B2
Dibenz[a,h]anthracene - B2
Fluoranthene - D
Fluorene - D
Indeno[1,2,3-c,d]pyrene - B2
Naphthalene - D
Phenanthrene - D
Pyrene - D

The above classifications have been verified by the Carcinogen Risk Assessment Verification Endeavor (CRAVE) and risk assessment summaries can be found on IRIS.

References:

Neal, J. and R.H. Rigdon. 1967. Gastric tumors in mice fed benzo(a)pyrene - A quantitative study. Tox. Rep. Biol. Med. 25: 553-557.

NTP (National Toxicology Program). 1980. Unpublished subchronic toxicity study: Naphthalene (C52904), Fischer 344 rats. Prepared by Battelle's Columbus Laboratories under Subcontract No. 76-34-106002. March.

Thyssen, J., J. Althoff, G. Kimmerle and U. Mohr. 1981. Inhalation studies with benzo(a)pyrene in Syrian golden hamsters. J. Natl. Cancer Inst. 66: 575-577.

U.S. EPA. 1988. 13-week mouse oral subchronic toxicity study. Prepared by Toxicity Research Laboratories, LTD., Muskegon, MI for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1989a. Mouse oral subchronic study with acenapthene. Study conducted by Hazelton Laboratories, Inc., for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1989b. Subchronic toxicity study in mice with anthracene. Conducted by Hazelton Laboratories, Inc., for the

Office of Solid Waste, Washington, DC.

U.S. EPA. 1989c. 13-week mouse oral subchronic toxicity study. Prepared by Toxicity Research Laboratories, LTD., Muskegon, MI for Office of Solid Waste, Washington, DC.

U.S. EPA. 1989d. Mouse oral subchronic toxicity with pyrene. Study conducted by Toxicity Research Laboratories, LTD., Muskegon, MI for the Office of Solid, Washington, DC.

TABLE 1

Oral RfDs for PAHs

Compound/ Status	Exposure	Species	Critical Effect	Uncertainty Factor	Modifying Factor	Reference Dose	Reference
Acenapthene / Verified (11/15/89)							
	175 mg/kg/day daily by gavage for 90 days (NOAEL); 350 mg/kg/day (LOAEL)	Mouse	Hepatotoxicity	3000	1	6E-2 mg/kg/day	U.S. EPA, 1989a
Anthracene / Verified (11/15/89)							
	1000 mg/kg/day daily by gavage for 90 days (NOEL)(HDT)	Mouse	No effects	3000	1	3E-1 mg/kg/day	U.S. EPA, 1989b
Fluoranthene / Verified (11/15/89)							
	125 mg/kg/day daily by gavage via corn oil for 13 weeks (NOAEL); 250 mg/kg/day (LOAEL)	Mouse	Nephropathy, increased relative liver weights, hematological and clinical effects	3000	1	4E-2 mg/kg/day	U.S. EPA, 1988
Fluorene / Verified (11/15/89)							
	Gavaged via corn oil 125 mg/kg/day for 13 weeks (NOAEL); 250 mg/kg/day (LOAEL)	Mouse	Decreased RBC, packed cell volume and hemoglobin	3000	1	4E-2 mg/kg/day	U.S. EPA, 1989c
Napthalene							
	50 mg/kg/day in diet for 5 days/week for 13 weeks (35.7 mg/kg/day)	Rat	Decreased body weight gain.	10,000	1	4E-3 mg/kg/day	NTP study (1980)

TABLE 1 (cont.)

Oral RfDs for PAHs

Compound/ Status	Exposure	Species	Critical Effect	Uncertainty Factor	Modifying Factor	Reference Dose	Reference
Pyrene / Verified (11/15/89)							
	75 mg/kg/day by gavage via corn oil for 13 weeks (NOAEL)	Mouse	Nephropathy and decreased kidney weight	3000	1	3E-2 mg/kg/day	U.S. EPA, 1989d

HDT = Highest Dose Tested