MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

May 15, 1995

TO: File for Cobalt (CAS# 7440-48-4)

FROM: Dan O'Brien

SUBJECT: Initial Threshold Screening Level for Cobalt

The initial threshold screening level (ITSL) for cobalt is 0.2 µg/m^3 based on an 8 hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: AQD chemical files, IRIS, HEAST, ACGIH TLV Booklet, NIOSH Pocket Guide to Chemical Hazards, RTECS, NTP Management Status Report, EPB Library, IARC Monographs, CAS On-line and NLM/Toxline (1967-February 3, 1995), CESARS, Handbook of Environmental Data on Organic Chemicals, Patty's Industrial Hygiene and Toxicology, Merck Index and Condensed Chemical Dictionary.

Cobalt, a hard, grey-white metal, occurs naturally as a relatively rare component of the earth's crust (0.001%), and is produced primarily as a by-product of the mining and processing of copper and nickel ores (Lauwerys and Lison, 1994). Its principal uses include as permanent magnets, in high-strength, heat-resistant, hard metal (cemented carbide) and surgical implant alloys. It is also used as a binder, as a drier in paints, as a pigment, in oncological radiation therapy, and as a nutritive additive in animal feeds. An essential element in mammals, as a component of cyanocobalamin (vitamin B12), it is involved in erythropoiesis (ACGIH, 1995; ATSDR, 1992) .

The toxicological literature concerning cobalt is extensive. While many studies have been conducted in a variety of laboratory species eliciting health effects in a number of different organ systems (CESARS, 1994; ATSDR, 1992), a substantial amount of human occupational data also exists. Given the established preference for human data (to avoid uncertainty inherent in extrapolation from animal studies) in the development of human health risk assessments (EPA, 1990), as well as kinetic studies demonstrating significant and sometimes marked interspecies differences in the lung clearance of cobalt (Patrick et al., 1994; Kreyling et al., 1991; Bailey et al., 1989), human data will be used in the derivation of the ITSL. Regarding the kinetic studies, briefly, cooperative groups of laboratories in Europe and the U.S. used common materials and methods to investigate the clearance of cobalt from the lungs of mice (CBA/H), Syrian hamsters (DSN), rats (3 strains: HNT, F344 SPF and Sprague-Dawley), guinea pigs (Harwell), beagle dogs, baboons and humans (Bailey et al., 1989); rats (HMT), beagle dogs and baboons (Kreyling et al., 1991); or Syrian hamsters, rats (2 strains: HMT and F344), guinea pigs (Harwell), beagle dogs and a baboon (Patrick et al., 1994). The two former studies exposed the subjects to cobalt oxide via inhalation,

while the latter used cobalt chloride or nitrate and intratracheal instillation. While the rankings of the relative rapidity of clearance among the various species differed between studies, in all cases the interspecies clearance rates were highly significantly different statistically. In the study which included human subjects (Bailey et al., 1989), humans were found to clear cobalt from the lungs the slowest, retaining 45% of 0.8 µm particles and 56% of 1.7 µm particles initially deposited in the lungs six months after termination of exposure. In contrast, after six months, HMT and Sprague-Dawley rats retained the least of any species studied, 1% and 8% of 0.8 µm and 1.7 µm particles, respectively. Although the human sample size was small (n = 2), to the extent that adverse respiratory effects in humans are related to residence time of cobalt in the lung, these data suggest that the use of animal data may not be appropriate in assessing the risk of cobalt exposure to humans, especially since adequate human data are available.

Carcinogenicity, mutagenicity and teratogenicity: The International Agency for Research on Cancer (IARC) has concluded that there is inadequate evidence of the carcinogenicity of cobalt in humans, but either sufficient or limited evidence of carcinogenicity in animals, depending on the chemical species and route of exposure (IARC, 1991). Although no evidence exists for the carcinogenicity of cobalt metal or compounds via oral or inhalation exposure in mammals (Lauwerys and Lison, 1994), animal experiments have demonstrated that single or repeated intramuscular, subcutaneous or intraperitoneal injections, as well as intramuscular cobalt implantation, may give rise to injection-site rhabdosarcomas, pleomorphic rhabdomyofibrosarcomas and fibrosarcomas (ACOIH, 1995; Nordberg, 1994; ATSDR, 1992; IARC, 1991; Jensen and Tüchsen, 1990; Léonard and Lauwerys, 1990). Intratracheal administration of cobalt oxide produced lung tumors in rats, but not in hamsters (Léonard and Lauwerys, 1990). Despite heavy occupational exposure to cobalt in humans, available studies have documented few cases of cancer, and there is insufficient evidence to classify cobalt as even a probable human carcinogen at this time (Lauwerys and Lison, 1994; Nordberg, 1994; Jensen and Tüchsen, 1990; Léonard and Lauwerys, 1990). The few epidemiological studies available have either found no statistically significant increases, or have used study populations with significant confounding exposures to arsenic and nickel, both known human carcinogens. It can be added that no fibrosarcomas were observed in hundreds of patients with prosthetic implants made of an alloy containing cobalt, chromium and molybdenum (Léonard and Lauwerys, 1990).

Cobalt metal and its compounds display only weak mutagenic properties (Léonard and Lauwerys, 1990), mainly in yeasts and plants (Jensen and Tüchsen, 1990), although positive results have been observed for divalent cobalt in some mammalian test systems, concerning interaction with DNA, sister chromatid exchanges in human lymphocytes, and hamster cell transformations (Nordberg, 1994; ATSDR, 1992; IARC, 1991). There are no data available for humans in vivo (Nordberg, 1994).

With respect to developmental toxicity, the only compounds studied, cobalt chloride and cobalt acetate, seem to be devoid of teratogenic activity (Léonard and Lauwerys, 1990). In the few cases where developmental effects have been noted following oral exposure, doses were in the range causing maternal toxicity (ATSDR, 1992; Léonard and Lauwerys, 1990). No obvious birth defects were noted in the fetuses of pregnant women treated with cobalt chloride at doses up to 0.6 mg cobalt/kg/day for 90 days to counteract anemia and low hemoglobin concentrations (ATSDR, 1992).

Thus, the available data do not support the use of carcinogenic or teratogenic endpoints as critical effects of cobalt exposure in humans, nor their use to drive derivation of a screening level.

Other health effects: For the general population, the diet represents the main source of cobalt exposure, although occupational exposures occur mainly by the dermal and inhalation routes (Lauwerys and Lison, 1994). With respect to the dermal route, cobalt is usually one of the four most common contact allergens for the general population. Cobalt hypersensitivity is often combined with sensitization to nickel (Nordberg, 1994), and simultaneous allergy to nickel may potentiate cobalt dermatitis (Veien et al., 1987). A small clinical trial by Veien and coworkers (1987) demonstrated the fact that individuals skin-sensitized to cobalt can have allergic reactions elicited by a systemic exposure to nickel. It should be pointed out that this reaction occurred in only one of the twelve cobalt-sensitized individuals studied, and the challenge which provoked the allergic response was oral rather than inhaled. Nevertheless, it seems prudent to note the fact that cross-reactivity between cobalt and at least one other metal occurs, as well as the possibility that an inhalation exposure to nickel could conceivably result in provocation of an allergic reaction in cobalt-sensitized individuals. Among nickel-sensitized individuals in this study, orally administered cobalt provoked an allergic reaction in eight of eighty-six exposed. While Lauwerys and Lison (1994) purport that "... absorption through the skin is low and the contribution by this route is probably negligible in comparison with that of the pulmonary and oral routes", Nordberg (1994) has noted that "the relative occurrence of exposure to cobalt by various exposure routes other than inhalation can also be assumed to be of importance for the relative occurrence of respiratory effects and systemic toxicity".

The literature reports extensive documentation of health effects resulting from inhalation exposure to cobalt and cobalt compounds, mainly from occupational studies of workers in cobalt and hard metal production, diamond polishing, and in those exposed to cobalt containing pigments (e.g., from decoration of Delft ceramics) (Lauwerys and Lison, 1994; ATSDR, 1992). While hypothyroidism, myocardial effects, and hematopoietic effects have all been reported, the effects of cobalt on the respiratory tract are recognized as critical effects (ACGIH, 1995; Nordberg, 1994; ATSDR, 1992) and are likely to be immune-related (Cirla, 1994; Sabbioni et al., 1994; Shirakawa et al., 1989; Shirakawa et al., 1988; Kusaka et al., 198G). Individuals with existing allergic and other respiratory diseases (especially asthma) may be considered especially vulnerable (WHO, 1986). These respiratory effects take a variety of forms, ranging from irritation of mucous membranes and the upper respiratory tract, to allergic asthma, and pulmonary alveolitis and interstitial fibrosis, the latter malady generally being referred to as "hard metal disease". With the exception of irritation (which occurs in all subjects exposed to sufficiently high cobalt concentrations), the occurrence of these manifestations is thought to fundamentally involve a component of individual susceptibility (Chiappino, 1994). This is supported by the low prevalence of asthma and interstitial lung disease (ILD), even among individuals exposed to substantial (in the mg range) concentrations of cobalt (Nordberg, 1994); estimates of prevalence for cobalt asthma range from 3 to 16% of exposed workers (Cirla, 1994), and two well-conducted studies (Sprince et al., 1988; Kusaka et al., 198G) estimated the prevalence of hard metal disease in their studied populations at 3 to 4% and 0%, respectively. Obstructive ventilator changes (i.e., ILD) have been reported to occur at cobalt exposures of 10-150 $\mu g/m^3$, while irritation of mucous membranes may

occur at 5-10 µg/m^3 (Nordberg, 1994). Occurrences of cobalt asthma have been reported in response to concentrations of < 5 µg/m3, (Sprince et al., 1988; Demedts et al., 1984) although the quality of the exposure assessments in these studies varies [see below]. Considering the pathogenesis of allergic asthma, and the fact that once sensitized, minute amounts of exposure can provoke an allergic reaction, it is not surprising that cobalt concentrations at or below the levels which cause irritation can also produce serious allergic reactions in susceptible individuals. The available data suggest that cobalt asthma is the most sensitive endpoint with respect to human health risk.

While the dose/response relationship between cobalt exposure and the occurrence of asthma has not been well characterized (Nordberg, 1994), the clinical picture of cobalt asthma has been well documented. Despite the mixed exposures experienced by workers, bronchial provocation tests and the isolation of cobalt-specific IgE antibody from individuals with clinical asthma have clearly demonstrated that cobalt is the causal agent (Chiappino, 1994; Cirla, 1994; Lauwerys and Lison, 1994; Shirakawa et al., 1989; Shirakawa et al., 1988; Kusaka et al., 198G). Moreover, it has also been demonstrated that tungsten carbide, a confounding exposure in many occupational studies, is not the causal agent of the asthmatic reactions (Cirla, 1994). Allergic reactions can be immediate (onset within 20 minutes), late (onset after 30 minutes), or dual (both) following exposure to cobalt (Shirakawa et al., 1989). This variable onset, coupled with the fact that cobalt-specific IgE has been isolated from some, but not all, cobalt asthmatics with positive reactions to cobalt provocation tests, has led to speculation that there may be more than one series of immunological events that finally result in overt cobalt asthma (Cirla, 1994). Reactions involving cobalt-specific IgG, and cellular interactions among lymphocytes, eosinophils and macrophages may all be involved in the dual and late responses. Cirla and coworkers have proposed these late cellular interactions as precipitating the inflammatory events that ultimately result in “fibrosis alveolitis” (i.e., ILD, “hard metal disease”). Although further research concerning these pathogenic events is necessary, this hypothesis appears to be a plausible explanation accounting for the element of individual susceptibility noted in all of the non-irritative respiratory effects due to cobalt. There is evidence to suggest that macrophages may directly link cobalt uptake with clinical disease. “The macrophage has a critical central role in the pathogenesis of fibrosis alveolitis” (Cirla, 1994), as well as a central (Kreyling et al., 1991; Bailey et al., 1989), perhaps rate-limiting (Patrick et al., 1994), role in the absorption and clearance of cobalt particles deposited in the lung. In light of the interspecies differences in cobalt kinetics previously discussed, such differences could be quite relevant to the actual appearance of adverse health effects, suggesting once again that animal studies may not be appropriate for use in assessment of risks to human health from cobalt inhalation.

Three studies document cobalt lung disease in workers exposed to < 10 µg/m^3 of cobalt. Since these studies demonstrate occurrence of the critical effect at the lowest cobalt concentrations reported in the reviewed literature, they may be viewed as potential key studies to identify a lowest observed adverse effect level (LOAEL) for derivation of the ITSL. The first (Demedts et al., 1984) is a case series which describes respiratory signs in five diamond polishers exposed to cobalt dust abraded off of polishing disks, the surface of which was composed of microdiamonds cemented into a matrix of fine cobalt. A cobalt concentration of 1.18 µg/m^3 is reported in the filtered air associated with one of the patients, as measured by atomic absorption photometry on air samples gathered via a suction pump. These authors

do not state whether the sample was taken in the breathing zone. They state that samples were obtained when an exhaust system, installed two years previously, was functioning optimally, and that, as a consequence, sampling results may have underestimated actual exposure of the workers. In addition, although some of the reported symptoms and the absence of lung fibrosis on biopsy were consistent with cobalt asthma, no bronchial provocation tests were performed to specifically diagnose the condition. The symptoms of the case series as a whole were consistent with hard metal disease. All respiratory signs were concluded by the authors to be due to cobalt, as it was essentially the only exposure of consequence, other than the diamond dust.

The second study, that of Sprince and coworkers (1988) was a cross-sectional study of 1,039 tungsten carbide production workers at 22 sites from 1983-1985. Worker exposure to cobalt was assessed with breathing zone samples (obtained at each major step of the production process) used to determine time weighted average (TWA) concentrations, and high volume samplers used to determine short-term exposure levels (STELs). Sample sizes were 194 for TWA determinations and 273 for STEL determinations. Cumulative exposures (in $\mu g/m^3$-yr) for each studied worker were calculated as [years in an operation x TWA cobalt air concentration of that job operation at the time of the study] and summed over all of the job operations performed by each subject. Average lifetime exposure (in $\mu g/m^3$) was determined as [cumulative exposure + total duration of exposure]. Health data obtained for each subject included medical and occupational histories, spirometry, carbon monoxide diffusing capacity and chest radiographs. The lowest average lifetime exposure associated with the diagnosis of ILD was 3 $\mu g/m^3$ for a nonsmoking female Etcher, employed for 7 years. Unfortunately, no bronchial provocation tests were performed to diagnose cobalt asthma in this subject. These authors did determine that the relative odds of “work-related wheeze” doubled when lifetime average cobalt exposure exceeded 50 $\mu g/m^3$, as compared with exposure ≤ 50 $\mu g/m^3$, though they also took care to point out that “work-related wheeze” should not be considered synonymous with cobalt asthma, the latter being considered a subgroup of those suffering from “work-related wheeze”.

The third and final study (actually a series of papers by the same investigators: Shirakawa et al., 1989; Shirakawa et al., 1988; Kusaka et al., 1986a,b) consisted of results of longitudinal health surveillance of a cohort identified in an earlier cross-sectional study (Kusaka et al., 1983; Kusaka et al., 1982). The cohort, consisting of all 282 workers exposed to hard metal at a hard metal factory employing ~1500, were examined annually by a team of thoracic specialists in Osaka, Japan between 1981 and 1984. The examinations included respiratory questionnaires, chest radiographs, spirometry and routine physical examination. Subjects whose radiographs showed opacities indicative of pulmonary disease were transferred to hospital for a more extensive evaluation which included lung biopsy, more spirometry, and a battery of blood tests which emphasized immunological tests. These tests included differential immunoglobulins, and specific IgE determinations for cobalt and a number of common environmental allergens. From these, a subset of asthmatics was identified and extensively tested for the causes of their asthma; these investigations are documented in great detail (Shirakawa et al., 1989; Shirakawa et al., 1988). Exposure to cobalt was assessed on at least one working day for every worker exposed during the study period, during which there were no pronounced changes in the production processes or methods at the factory. Total dust or mist breathing zone samples were collected with a mean sampling

time of six hours during a workday, and their cobalt content determined by atomic absorption spectrophotometry (AAS) with detection limits of 0.1 mg/m^3 and 1 μg/$m^3$for total dust and cobalt, respectively. Aerodynamic size distribution of the airborne particles in a shaping room was estimated via an Andersen sampler, and work area hard metal dust samples were collected at head height on glass fiber filters and analyzed for cobalt content by AAS; these samples were collected over six hour periods on five consecutive days. Area cobalt concentrations ranged from the detection limit to 6388 μg/m^3; the lowest reported mean cobalt concentration to which a cobalt asthmatic was exposed was 7 μg/m^3. The clinical asthma of this subject, a 51 year old Grinder who smoked 0.5 a pack/day of cigarettes, was confirmed to be due (at least in part) to cobalt by positive bronchoprovocation tests with cobalt chloride, and by positive cobalt-specific antibody (Farr) tests. The authors note, with respect to these subjects that "as all of them wear respirators, the actual uptake of cobalt is much less than the amount found in the breathing zones". Consequently, it is plausible that a cobalt concentration even lower than the 7 μg/m^3measured in the breathing zone of this subject was enough to elicit clinical disease.

Despite this substantial evidence that cobalt asthma can occur at exposures of < 10 μg/$m^3$of cobalt, there are a number of serious difficulties which must be addressed in order to use these as key studies/LOAELs for derivation of an ITSL. First, all three of these studies involved mixed exposures. In the case of the diamond polishers (Demedts et al., 1984), the subjects were exposed to cobalt and diamond dust; in the case of the hard metal workers (Sprince et al., 1988; Kusaka et al., 1986a), in addition to cobalt, the workers were exposed to other components of hard metal (tungsten, titanium, vanadium et al.) . While there is little evidence to suggest that these other exposures are in themselves sufficient to cause asthmatic reactions (the inability of tungsten, e.g., to do so has already been noted), there is evidence to suggest that tungsten, and possibly others, may modulate the ability of cobalt to cause pulmonary disease by affecting cobalt's bioavailability and subsequent uptake (Lauwerys and Lison, 1994; Nordberg, 1994). Second, there is uncertainty surrounding the chemical form of cobalt which is causal for asthma. Results of the extensive immunological investigations conducted by the Japanese group (Shirakawa et al., 1989; Shirakawa et al., 1988) suggest that, unlike asthma caused by platinum, chromium and nickel, cobalt must be converted from an alloy to the ionized form on the bronchial mucosa in order to act as a hapten (following conjugation with proteins), and so cause asthma. Third, many of the cobalt asthmatics were either smokers, on anti-asthmatic medication, or both, at the time these studies were conducted. It is extremely difficult, given the available data, to assess the magnitude and direction of the modifying force these factors might have on the environmental concentration of cobalt necessary to induce asthma. For example, in the Sprince et al. (1988) study, a logistic regression analysis found that current smoking status had greater influence on the probability that a worker had symptoms of "work-related wheeze" than did the worker's present exposure to > 50 μg/m^3vs. ≤ 50 μg/m^3 of cobalt. Further, concurrent use of anti-asthmatic medications could plausibly allow a sensitized individual to remain asymptomatic while exposed to cobalt concentrations that would normally provoke an asthmatic reaction. Finally, the classic difficulties, encountered in exposure assessment enter in as well. Even in an excellent study such as that of Kusaka and coworkers (1986a,b), the theoretically most sensitive worker discussed above had a latency of 20 years between first exposure to hard metal and the actual development of clinical cobalt asthma. While the authors note no major process changes having occurred during the four years of the study that could have changed the prevailing cobalt

concentrations to which this worker was exposed, it is impossible to tell what levels of cobalt s/he was exposed to prior to the study, and it seems likely, given the history of industrial hygiene, that they would have been higher.

Unfortunately, given the data currently available, the confounding effect of these and possibly other factors cannot be adequately assessed at this time. Moreover, EPA (EPA, 1990) has noted that "some agents may not be suitable for either chronic or subchronic RfC estimation.... An example of such compounds are those that cause occupational asthma or induce hypersensitivity reactions". Given these constraints and those of the Air Toxics rules, it seems unwise to use these studies in the derivation of a screening level. Alternatively, an RfD is not available for cobalt, and even if it was, the fact that respiratory effects are critical for this chemical would make it inappropriate to use oral data when inhalation exposure data are available.

As cited previously, a draft documentation of the recently revised American Conference of Governmental Industrial Hygienists Threshold Limit Value (ACGIH TLV) for cobalt is available (ACGIH, 1995). The TLV for cobalt is currently 0.02 mg/m^3. While extensively documented and obviously based upon health effects, the TLV documentation addresses the critical effect (cobalt asthma) only cursorily as one of a number of possible health effects. Nonetheless, considerable experience with occupational exposures to cobalt is reflected in the TLV, and an ITSL derived from the TLV would be more than an order of magnitude below the lowest cobalt concentration linked specifically with cobalt asthma in Kusaka's work (7 µg/m^3). This would allow for more than a ten-fold uncertainty factor to account for humans presumably more sensitive than healthy workers, and for variations in duration of exposure. Considering the low prevalence of cobalt asthma in even heavily exposed populations, the extreme variability in the exposure concentrations and durations reported to provoke clinical asthma, and the previously mentioned uncertainties associated with the LOAELs for cobalt asthma currently available, use of the TLV as an Occupational Exposure Limit (OEL) to drive the derivation of an ITSL seems a reasonable course of action.

It should be noted that while Rule 232(1) (c) provides for the use of the 1988-1989 ACGIH TLVs (rather than the current TLV5) as OELs, Rule 230(8) (b) allows for the use of an alternative methodology for determining the ITSL if it is more appropriate on toxicological grounds and supported by the scientific data. The TLV in 1988-1989 was 0.05 mg/m^3. The draft TLV documentation (ACGIH, 1995) notes that cobalt concentrations of <0.1 mg/m^3 have "caused asthma and changes in pulmonary function" and that "transient myocardial changes have been reported at exposure concentrations below 0.06 mg/m^3" (in other words, at or below the level of the 1988-1989 TLV) . Moreover, adverse respiratory effects have been reported associated with cobalt exposures of < 10 µg/m^3 (0.01 mg/m3) as detailed above in the work of Sprince and Kusaka. Clearly, the scientific data support the use of the current TLV (0.02 mg/m^3) in preference to the 1988-1989 value for derivation of the ITSL.

ITSL Derivation: Per Article II, Chapter 1, Part 55, Rule 230(8) (b) of Act 451:

$$\boldsymbol{ITSL} = OEL\, x \frac{1}{100} = 0.02 \frac{mg}{m^3}\, x \frac{1}{100} = 0.0002 \frac{mg}{m^3}\, x \frac{1000 \mu g}{1\, mg} = \mathbf{0.2\ \mu g/m^3}$$

where the factor of 1/100 is a safety factor to account for: 1) differences in susceptibility between the healthy, adult worker population as compared to the general population which may include individuals or subpopulations more sensitive to the effects of exposure to cobalt and 2) the difference in exposure duration for the worker population as opposed to the general population. The factor is derived as follows:

$$\text{Safety factor } = \frac{40 \text{ hours}}{168 \text{ hours}} x \frac{30\ years}{70\ years} x \frac{1}{10} = \frac{1}{100}$$

The first factor adjusts for the difference between a 40 hour work week and the total hours in a week; the second factor adjusts for the difference between an assumed working life of 30 years and an assumed total lifespan of 70 years; and the third factor is a standard ten-fold uncertainty factor to extrapolate from the healthy worker to sensitive individuals in the general population.

Consistent with 232 (2) (a), since the OEL used here is based on an eight hour time-weighted average, an **8 hour averaging time** is considered appropriate.

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