MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

September 27, 1999

TO: File for Vanadium Pentoxide (CAS 1314-62-1)

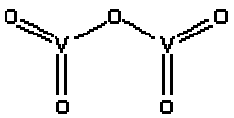
FROM: Dan O'Brien, Toxics

SUBJECT: Initial Threshold Screening Level for V205

The initial threshold screening level (ITSL) for V205 is 0.5 µg/m³ based on a 1-hour averaging time.

The following references or databases were searched to identify data to determine the ITSL: AQD chemical files; EPA's Integrated Risk Information System (IRIS) and Health Effects Assessment Summary Tables (HEAST); American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Value (TLV) Booklet; National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Chemical Hazards and Registry of Toxic Effects of Chemical Substances (RTECS); National Toxicology Program (NTP) World Wide Website (WWW), MDEQ Library; International Agency for Research on Cancer (IARC) WWW; Chemical Abstract Service (CAS) On-line and National Library of Medicine (NLM) Toxline (1967-September 20, 1999), Chemical Evaluation Search And Retrieval System (CESARS), Patty's Industrial Hygiene and Toxicology, Merck Index and the Condensed Chemical Dictionary.

Figure 1.



V2O5 is a yellow to red brown orthorhombic crystalline solid (Hawley, 1981; Merck, 1983). The compound's molecular structure (CambndgeSoft, 1999) is displayed in Figure 1. Its primary industrial use is in the production of ferrovanadium for corrosion resistant alloys used for spring and high speed tool steels. Vanadium (V) lends itself nicely to this application due to its ability to form extremely strong carbides, stronger even than those of tungsten (Beliles, 1994; CESARS, 1997). Other uses include: as a catalyst in sulfuric acid manufacturing and in many organic reactions (olefin polymerization and high temperature); as an inhibitor of ultraviolet light transmission in glass and in the manufacture of yellow glass; as a colorant for ceramics; as a photographic developer; and as a mordant in the dyeing and printing of fabrics (Hawley, 1981; Merck, 1983; Beliles, 1994). In addition, V is found in fuel oils at concentrations of 250-400 ppm, so potentially hazardous exposures to V2O5 can occur during the cleaning of oil-fired boilers and from oil refinery furnace soot. Indeed, some of the classic occupational medical data stem

from exposures and intoxications that have occurred in these job settings (ACGIH, 1992; Beliles, 1994). V2O5 has also been used historically as a therapeutic agent in the treatment of syphilis (Proescher et al., 1917), tuberculosis, chlorosis and diabetes (Beliles, 1994).

A great deal of toxicological data on the effects of exposure to V compounds has accumulated due to the regular application of the metal in industrial processes. Recent reviews of the toxicology of the V compounds, emphasizing V205, have been published (ATSDR, 1992; Waldron and Scott, 1994; Basilico and Garlanda, 1995). A summary of the ecotoxicity of V compounds is also available in outline form (CESARS, 1997) ATSDR has published a Toxicological Profile for vanadium (ATSDR, 1992) which provides extensive documentation of the literature current to that date. Because of the comprehensiveness of that document, and in the interest of brevity, information contained in it will not be repeated here. The interested reader is referred to it for a more comprehensive treatment of the health effects and public health significance of V compounds. In summary, while this document (and others) point out that multiple toxicological effects have occurred in animals following V exposure, both epidemiological and animal toxicology studies have demonstrated that the target organ system for inhaled V compounds is the respiratory system. With that in mind, ATSDR has derived an acute-duration inhalation Minimal Risk Level (MRL of 0.0002 mg/m^3 (O.2g/m3). The MRL is defined as an estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious non-cancer effects over a specified duration of exposure (ATSDR, 1992). ATSDR intends acute MRLs to be relevant to exposures lasting less than 14 days. Neither intermediate duration (applicable to exposures lasting 15-365 days) nor chronic duration (for exposures of >1 year) inhalation MRLs were derived for V because of lack of quantitative exposure data.

Brief mention of the acute toxicity of V205 should be made. In the summary of Basilico and Garlanda (1995), the oral lethal dose 50 (L) in mice by gavage is listed to be 23.4 mg/kg body weight. The lethal concentration 50 (LC) in rats exposed for 1 hour was 70 mg/m^3; notably, an exposure concentration less than an order of magnitude lower (10 mg/m^3) was reported to be “the minimum concentration of “V2O5 that caused mild signs of acute poisoning”. Concentrations of 114 mg/m^3 resulted in the death of half the rabbits exposed for 7 hours (Sjöberg, 1950; ATSDR, 1992). In contrast, two 6 hour exposures to cynomolgus monkeys spaced 1 week apart at a concentration of 4.4 mg/m^3 (2.5 mg V /m^3) was sufficient to cause significant lung function decrements (Knechtet al., 1985; ATSDR, 1992). These data suggest two relevant points, viz., that the dose/response curve of V205 is relatively steep, and that there is substantial interspecies variability in sensitivity to the acute toxicity of V205.

Given that the target organ for inhaled V compounds is the respiratory system, the remainder of this memo will largely focus on respiratory effects. Moreover, because substantial human epidemiological data documenting the effects of exposure toV2O5 are available, emphasis will be placed there. While there is general agreement on the anatomical target of V toxicity, the variety of clinical signs exhibited in various studies and exposure scenarios leaves open to debate the pathophysiological mechanism involved. There also seems to be some agreement that the toxicity of V205 fume exceeds that of V205 dust, presumably because the smaller particle size allows deeper penetration into the lung (NIOSH, 1978; Beliles, 1994; Basilico and Garlanda, 1995). NIOSH (1978) interprets this to mean that “similar effects from the fume (as compared to those from dust exposures) could be expected at lower concentrations”.

Inhalation exposure to V compounds (most often reported in the literature as V205) results in respiratory disease, the clinical presentation of which has been well documented in the medical literature for most of the twentieth century (Dutton, 1911; Gul'ko, 1956; Lewis, 1959; Zenz et al., 1962). Wheezing and dyspnea on exertion are considered the most characteristic signs, along with throat irritation. Other clinical signs reported include conjunctival and nasal irritation, cough (with or without sputum production), sneezing, epistaxis/hemoptysis, and various other non-specific complaints (headache, fatigue, nausea, etc.). A greenish-black discoloration of the tongue accompanied by a metallic taste have been described as characteristic. Dermatologic signs (itching, rash, green discoloration of the skin) have also occasionally been reported. A good example of the spectrum of clinical signs has been presented by Levy et al. (1984) in their study of occupational vanadium intoxication that accompanied a fuel source conversion from oil to coal at an electric power plant. These signs are accompanied by moderate pathological changes characterized by acute to chronic epithelial hyperplasia in affected tissues. Chronic atrophic epithelial changes have also been reported. The airways appear to be more affected than the pulmonary parenchyma (Musk and Tees, 1982), and the majority of studies have shown minimal to no lesions on chest radiographs of V intoxicated patients (Kiviluoto, 1980; Levy et al., 1984). The disease tends to consist of acute, relapsing episodes, which subside over a period of days to weeks after withdrawal from exposure (Zenz and Berg, 1967; Musk and Tees, 1982; Levy et al., 1984) although constant coughing can occur. Duration can be a few days to more than two months. Onset has generally not been described as immediate; typically, illness begins anywhere between several hours to a few days after exposure commences. Controlled exposures of human volunteers in exposure chambers have shown these clinical signs, in general, to be dose-related, with irritation and increased mucus production noted at V205 concentrations as low as 0.1 mg/m^3 for an eight hour exposure (Zenz and Berg, 1967). Those same authors found that the intensity of signs and rapidity of their onset were magnified by subsequent exposures. In general, those studies that have measured systemic clinical pathology endpoints (e.g., hematology, serology, V concentrations in excreta) have not recorded substantial deviations from normal (Zenz and Berg, 1967; Kiviluoto et al., 1981).

While the symptomatology of V intoxication is by now well characterized and agreed upon, there is still debate concerning whether the pathophysiological mechanism that induces it is one purely of irritation, or one of hypersensitivity. It has been noted that V compounds appear to be capable of inducing asthma in previously normal subjects (Musk and Tees, 1982; Bernstein, 1992; Beliles, 1994). The symptomatology and course of this aspect of the disease has been discussed at length by Sjôberg (1951, 1956). In general, Sjöberg's work suggests that asthmatic responses, with or without skin hypersensitivity, have occurred following repeated exposure to concentrations greatly in excess of the recommended workplace exposure limits (which, were 0.5 mg/m^3 at the time of Sjöberg's investigations). In some instances, exposure concentrations attained values 150 times (75 mg/m^3) that limit. Because the clinical course was characterized by onset a few days to a week after repeated exposures began, it has been suggested that delayed hypersensitivity was occurring. In contrast, other authors (Basilico and Garlanda, 1995) report that even brief exposures cause rhinorrhea, epistaxis, dyspnea and acute asthmatic bronchitis". These signs have been documented to progress to bronchial or lobar pneumonia in some cases. In a follow up study, Sjöberg (1956) noted that some subjects still had persistent bronchitis resembling asthma with bouts of dyspnea and fatigue 8 years after their first exposure, in spite of the fact that occupational exposures had decreased substantially, suggesting that high exposures to V205 are capable of precipitating chronic disease, and lending support to the observation that the severity of the disease worsens with subsequent

exposures. Notably, however, Sjöberg found no evidence of either pneumoconiosis or emphysema; nor, apparently, have any of the other authors who have looked for those sequelae.

In contrast to the findings of these investigators, however, ACGIH (1992) has noted that others "have been unable to confirm any evidence of immunologic changes in respiratory tract tissues of vanadium workers", thus casting doubt on whether the observed respiratory disease is truly a hypersensitivity reaction. The key piece of clinical evidence in the asthma debate appears to be the equivocal nature of the pulmonary function testing results from the accumulated studies While some occupational studies have demonstrated spirometric decrements following V205 exposure that were consistent with hypersensitivity (Musk and Tees, 1982; Levy et al., 1984), others have found essentially normal results in patients otherwise exhibiting the other classic signs of V intoxication (Zenz and Berg, 1967; Kiviluoto, 1980). A group of investigators who were able to induce pulmonary function deficits in monkeys with V205 (Knecht et al., 1985) have argued that these negative findings in humans were attributable to poor timing of the spirometry exams, an observation which may be valid[1]. Zenz and Berg (1967) performed their pulmonary function tests immediately after termination of their subjects' exposures, but did not repeat them several hours later when clinical signs had become more severe, and Kiviluoto (1980) measured pulmonary function on his occupational cohort at the end of their summer holiday, a time at which they were presumably less symptomatic than during exposure. Kiviluoto's negative results do suggest that V exposure does not result in permanent pulmonary function deficits as long as previously intoxicated individuals avoid re-exposure. Clearly, however, this does not rule out the possibility that subclinical asthma may be present as a permanent adverse effect. It should also be mentioned that, building on their previous findings, Knecht and colleagues (1992), found that subchronic exposures to V205 did not induce allergic sensitization in cynomolgus monkeys at exposure concentrations consistent with realistic human occupational exposures. They also noted a trend toward decreased pulmonary reactivity in the animals after subchronic exposures, suggesting that tolerance to exposure can be brought on by repeat exposures. Knecht's work has pointed out the value of the monkey as an animal model for human pulmonary reactivity, as well. Thus, in summary, the question of whether V205 induces its adverse effects via hypersensitivity or merely via irritation remains unresolved. Notably, at the time of this writing, V205 is undergoing both a lifetime inhalation bioassay in rats and mice and immunotoxicity trials in monkeys conducted by NTP (1999). Hopefully, the results of these studies will shed considerable light on the issue.

Perhaps also worthy of brief mention here is the emerging role transition metals such as V are being found to play in the toxicity of fine particulate matter (see, e.g., Carter et al, 1997 and Dreher et al., 1997). While this is an area of very active research (TCPAPHH, 1999), the exact pathologic mechanism by which these effects occur has yet to be worked out, although the ability of these metals to generate reactive oxygen radicals has been speculated to play some role.

With respect to reproductive/developmental endpoints, in addition to the summary reviews previously noted, these effects have been specifically reviewed by Domingo (1996). That author found ample evidence that a variety of V compounds, including V205, are capable of causing

[1] Those authors speculated that the time delay between exposure Onset and clinical signs might be attributable (at least partially) to the time needed for solubilization of V205 dust particles in the respiratory mucosa.

both adverse reproductive and developmental effects in animals. While prominently noting the lack of toxicity information on the possible occurrence of such effects following inhalation exposures, reproductive (reduced sperm counts) and developmental (developmental delays, increased embryolethality, reduced fetal weight, cleft palates, skeletal defects) effects have been documented to occur following oral exposures ≥40 mg/kg-day and ≥5 mg/kg-day for reproductive and developmental endpoints, respectively. Exposures took place at various periods prior to mating, as well as during gestation and lactation. The interested reader is referred to Domingo (1996) for further details. Thus, while no data to date have characterized the reproductive or developmental effects of V205 following inhalation exposures, considering the greater absorption of V205 via the inhalation (as compared to the oral) route, the occurrence of such effects appears to be a reasonable possibility. Whether such effects, if they occur, would be likely to occur at exposure concentrations below, at, or greater than, the concentrations known to result in respiratory effects, remains to be determined.

While EPA has not established an inhalation Reference Concentration (RfC), it has developed an oral Reference Dose (RfD) for V205 (EPA, 1996). This RfD of 0.009 mg/kg-day was the basis for one of the two interim ITSLs previously derived for the compound in October 1992. It is based on an unpublished study by Stokinger and colleagues from 1953, in which an unspecified number of rats were exposed to vanadium in their diets for 2.5 years. Of the physiologic endpoints assessed, the only significant change reported was a decrease in the amount of cystine in the hair of the exposed animals at a dose of 179 ppm V205. The No Observed Adverse Effect Level (NOAEL) was determined to be 17.9 ppm. EPA assigned low confidence to the RfD "because of the lack of details... and the scarcity of data available on vanadium pentoxide." The Air Toxics Rules [R232(1)(b)] provide for ready use of the RfD in calculation of screening levels if available data do not indicate that extrapolation from the oral to the inhalation route of exposure is inappropriate. However, the preponderance of the available evidence suggests that the vanadium compounds are rather poorly absorbed orally, and the principal toxicological effects have been documented to occur following inhalation (ACGIH, 1992; ATSDR, 1992; Beliles, 1994; Basilico and Garlanda, 1995). Thus, the RfD, and other toxicity data based on oral exposures, likely are not representative of the potential inhalation toxicity of V205, and so are not an appropriate basis for derivation of a screening level.

In choosing data for screening level development, preference is generally given to human epidemiologic data or chronic laboratory animal inhalation studies which can be used to derive a Reference Concentration (RfC). It is conceivable that the existing occupational data could be used to derive an RfC. However, two principal factors suggest this would be a formidable and potentially contentious undertaking. First, there seems to be disagreement on whether the respiratory effects caused by V205 exposure are of a permanent nature. For example, while Beliles (1994) describes Sjöbergs (1956) findings as indicating that "V205 overexposure can lead to a chronic condition", ACGIH (1992), in contrast, states that "no ... permanent pulmonary ... dysfunction[s] have been linked to vanadium pentoxide exposure". Second, whether V205 exposure can lead to true respiratory hypersensitivity reactions needs to be definitively established. While reviews of the recent literature (Basilico and Garlanda, 1995) have stated that "even brief exposures cause ... asthmatic bronchitis", the pathophysiologic mechanism does not yet appear to have been established with sufficient confidence to indicate that these reported reactions are, in fact, true respiratory hypersensitivity. This is a key point, since true asthmatic hypersensitivity would not only indicate the presence of a chronic disease condition, but would also suggest that affected individuals, once sensitized, could become symptomatic at exposure

concentrations far below those that led them to become sensitized initially. Moreover, if V205 exposure indeed proves to induce respiratory hypersensitivity, derivation of an RfC from occupational data may no longer be appropriate[2]. Further, long term animal inhalation toxicity studies which could potentially also form the basis for an RfC are unavailable. Given these limitations, the decision has been made not to develop a RfC-based ITSL at this time.

When adequate data for RfC calculation are not available, next preference is given to oral data for calculation of a Reference Dose (RfD) if available data do not indicate that extrapolation from the oral to the inhalation route of exposure is inappropriate. As noted above, the disparities in absorption and toxicity between the oral and inhalation routes of exposure suggest that the use of oral data, even an RfD, would be an inappropriate basis for the ITSL for V205.

Occupational Exposure Limits (OELs) are designated as being the next preference as a data source for derivation of screening levels, and relatively speaking, those for V205 are rather well documented because of the substantial "OCCUPATIONAL MEDICINE"/toxicological literature devoted to V. ACGIH (1992) has published an eight hour time weighted average (TWA) Threshold Limit Value (TLV) of 0.05 mg/m^3 for both the fume and respirable dust of V205. In contrast, NIOSH (1997) has published separate RELs for the V205 dust and V205 fume. In contrast to the TLV, the RELs are ceiling limits (as opposed to being based on TWAs). The RELs for both the dust and fume of V205 are set at 0.05 mg/m^3 as well, suggesting basically concurring opinions on the part of NIOSH and ACGIH with respect to a protective exposure limit; only the time period over which that limit is applicable varies between the two agencies. While the issue of whether V205 is capable of inducing persistent respiratory hypersensitivity remains unresolved (and thus the OELs principally address prevention of the irritative effects of V205) an ITSL derived from either OEL would be more than two orders of magnitude below the lowest V205 concentration specifically documented to elicit respiratory symptoms [0.1 mg/m^3] (Zenz and Berg, 1967; ACGIH, 1992; Beliles, 1994; Basilico and Garlanda, 1995). Consequently, it is

[2] In its review draft of interim Methods for Development of Inhalation Reference Concentrations, EPA (1990) stated that "some agents may not be suitable for either chronic or subchronic RfC estimation because they act in a manner distinct from those agents whose action is concentration and/or time- dependent. An example of such compounds are those that cause occupational asthma or induce hypersensitivity reactions". It should be noted that this language was removed from the final RfC methods guidance, but specific, practical guidance in that document concerning how this problem should be addressed is vague to lacking (EPA, 1994a, pp. 2-40 - 2-42). EPA has provided some precedent on methods for deriving RfCs for agents that induce occupational asthma, e.g. the isocyanates (EPA 1994b, 1995. 1998), in the form of RfC assessments currently listed in IRIS. Two of three of the isocyanate RfCs are based on long term inhalation studies in animals. The third, that for 2,4/2,6-toluene diisocyanate (TDI), though based on epidemiological data, is extensively supported by long term animal inhalation studies, and laboratory studies in which assessment of respiratory/immunologic endpoints was specifically targeted. Similar studies for V2O5 are lacking. Moreover, the epidemiologic data which served as the key study for the TDI RfC were characterized by "several strengths not ordinarily found in investigations of this type" (EPA. 1995): (1) baseline spirometry values for each individual established prior to exposure; (2) parallel internal spirometry comparisons between study groups; (3) statistical techniques which assessed true annual change and interindividual variability in measurements; (4) an extensive number of breathing zone samples analyzed using extremely accurate measures; and (5) spirometric assessments of decrements due to smoking. The available epidemiological data for V2O5 all lack one or more of these characteristics. Notably. EPA has not derived inhalation RfCs based on evidence of respiratory hypersensitivity in human epidemiological studies for any of a number of other metals suspected of inducing occupational asthma (e.g., aluminum, cobalt, chromium, nickel). Finally, EPA has not itself derived a RfC for V205, possibly for lack of these types of data. While acknowledging the possibility that sufficient epidemiological data may already exist to derive a RfC for V2O5, in light of this overall lack of specific guidance, the decision has been made not lo develop a RfC independent of EPA until more and better data become available.

considered appropriate here to use the NIOSH REL for V205 (0.05 mg/m³, as a ceiling value) as the basis for the ITSL for V205. Consistent with R232(1)(c), the REL is used in preference to the ACGIH TLV, since, being a ceiling value, it is more protective than ACGIH's time weighted average TLV.

ITSL Derivation: Per Rule 232(1)(c), part 55, of Act 451, as amended:

ITSL = OEL x 1/100 = 0.05 mg/m³ x 1/100 = 0.0005 mg/m³ x 1000 µg/mg = 0.5 µg/m³

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 V205 and 2) the difference in exposure duration for the worker population as opposed to the general population.

The factor is derived as follows:

Safety factor =. 40hours/168hours x 30years/70years x 1/10

The first term 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.

Per 232(2)(a), since the screening level is based on an OEL with a ceiling exposure limit, a 1-hour averaging time applies to this ITSL. It should be noted that while this ITSL is slightly higher than the acute inhalation MRL (0.2 µg/m³) derived by ATSDR (1992), the two values are quite close. In addition, the MRL is intended to apply to "a daily exposure up to 14 days in duration", and so could be argued to be relevant to a 24 hour (or longer) averaging time, while the ITSL carries a 1-hour averaging time. This effectively makes the ITSL more protective than the MRL.

Finally, it should be reiterated that at the time of this writing, V205 is undergoing a comprehensive battery of animal toxicity testing by NTP (1999), which includes 2 year carcinogenicity and toxicokinetic studies in rats and mice, and immunotoxicity trials in monkeys, all by the inhalation route of exposure. The chronic bioassay will likely not only address the carcinogenicity of V205, but provide a potential basis for derivation of an inhalation RfC as well. It is strongly recommended that these results be reviewed in detail as they become available, and relevant data incorporated into revision of this screening level, as appropriate.

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