NIOSH Comments to OSHA

Comments of the National Institute for Occupational Safety and Health on the Occupational Safety and Health Administration Request for Information Occupational Exposure to Hexavalent Chromium (CrVI)

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U.S. Department of Health and Human Services
Public Health Service
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

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The National Institute for Occupational Safety and Health (NIOSH) has reviewed the Occupational Safety and Health Administration (OSHA) request for information on *Occupational Exposure to Hexavalent Chromium (CrVI)* published in the Federal Register (FR) on August 22, 2002 [67 FR 54389]. Our comments follow each bolded question from the FR request for information.

(1) What studies (including positive and negative studies) should OSHA consider useful in assessing the potential carcinogenic, mutagenic, and non-carcinogenic health risks of CrVI exposure? Explain your scientific rationale for recommending these studies including potential strengths and weaknesses such as size of the population (or sample) studied, characterization of exposure, and confounding factors.

NIOSH is currently in the initial stages of a multi-year project to update the 1975 hexavalent chromium (CrVI) criteria document [NIOSH 1975]. As part of this update, NIOSH is evaluating the scientific literature available on hexavalent chromium. NIOSH is not able to provide specific recommendations and study critiques at this time as the literature review and analysis are ongoing. Many of the questions posed by OSHA in this request for information will be addressed during the development of the revised criteria document. NIOSH will forward the revised document to OSHA upon completion.

(2) Are there any recent studies that examine the dermal effects of CrVI exposure?

Recent studies that examine the dermal effects of CrVI exposure include:

- Gibb HJ et al. [2000a]. Clinical findings of irritation among chromium chemical production workers. Skin irritation and ulcerated skin were reported in 15% and 32%, respectively, of workers first employed between 1950 and 1974 at a chromate production plant.

- Fowler JF Jr. et al. [1999]. An environmental hazard assessment of low-level dermal exposure to hexavalent chromium in solution among chromium-sensitized volunteers. Human volunteers immersed one arm in a 25 to 29 mg/L potassium dichromate bath for 30 minutes per day on 3 consecutive days resulting in acute perieccrine reactions but not allergic contact dermatitis.

- Corbett GE et al. [1997]. Systemic uptake of chromium in human volunteers following dermal contact with hexavalent chromium (22 mg/L). Human volunteers were immersed below the shoulders in 22 mg/L CrVI in water for three hours. CrVI was reduced to CrIII prior to systemic uptake.

- Liu KJ et al. [1997]. Reduction of carcinogenic chromium (VI) on the skin of living rats. These authors demonstrated the reduction of CrVI to reactive CrV species on the skin of rats.

A presentation on dermal effects, "Prevention of Contact Dermatitis by European Legislation," given at the International Conference on Occupational and Environmental Exposure of Skin to Chemicals: Science and Policy [September 8-11, 2002, Washington, DC], discussed the Nordic and European approaches to dealing with contact dermatitis due to CrVI in cement [Liden 2000]. National regulation in Nordic countries limits CrVI in cement to below 2 mg/kg through the addition of iron sulfate. In Europe, since July 2002, cement containing more than 2 mg/kg CrVI has required the label: "Contains chromium (VI). May produce an allergic reaction." The abstract and conference proceedings are available at the skin topic page on the NIOSH Web site: http://www.cdc.gov/niosh/skinpg.html

(3) Are there any studies showing adverse health effects resulting from routes of occupational CrVI exposure other than dermal contact and inhalation? What are those adverse health effects?

The most important routes of occupational exposure to CrVI are inhalation exposure and dermal contact. Oral occupational exposure to CrVI should be minimal if safe work practices are used. The reduction of ingested CrVI to CrIII prior to absorption should minimize any potential adverse effects of low dose oral exposure. Occupational epidemiologic studies that investigate adverse health effects other than lung cancer in CrVI-exposed workers are available. Correlation of these additional health effects with a method of exposure other than dermal contact or inhalation is problematic. Quantifying oral ingestion in the workplace relative to inhalation and/or dermal exposure is also difficult. A recent review article analyzes the historical occupational epidemiological studies that report digestive system cancer [Proctor et al. 2002]. Another recent review summarizes the available studies on oral exposure to CrVI [Flegal et al. 2001].

Barceloux [1999] recently reviewed various case reports of occupational and non-occupational CrVI ingestion. Adverse health effects seen in these cases include gastrointestinal symptoms, hypotension, and hepatic and renal failure. Most of these case reports involve lethal doses of CrVI.

Studies describing the voluntary ingestion of CrVI demonstrated that more than 99.7 percent of a 10 mg dose of CrVI in drinking water was reduced to CrIII before entering the bloodstream [Kerger et al. 1997].

(4) Are there any important studies related to the dose response behavior of CrVI, including cellular, mechanistic, and dosimetric considerations? For instance, are any health effects of CrVI dependent on the time period over which exposure

occurs rather than dependent on the total cumulative dose received or are there data that suggest CrVI exhibits a threshold effect?

A recent molecular study demonstrated dose-dependent cellular effects of CrVI including activation of nuclear transcription factors NF-kappaB and p53, DNA damage, induction of cell apoptosis, and inhibition of cell proliferation [Liu et al. 2001]. No thresholds to these cell responses were found at doses as low as 1 µM CrVI.

Steinhoff et al. [1986] administered sodium dichromate intratracheally to rats for 30 months. Doses were 0.01, 0.05, or 0.25 mg/kg, five times a week, or 0.05, 0.25 or 1.25 mg/kg once a week. The effects on chronic inflammation and tumor production were reported to be greater in the 1 x 1.25 mg/kg dose group than in the 5 x 0.25 mg/kg group, indicating that the effects were more dependent on the dose concentration than the weekly total dose.

Gibb et al. [2000b] is the most recent epidemiologic study to report a dose-response relationship between CrVI exposure and lung cancer. One of the animal studies that demonstrates dose-response relationships between exposure to CrVI and adverse effects is Glaser et al. [1985]. DeFlora [2000], in a recent review article, suggests that "All experimental and epidemiological data, and the underlying mechanisms, point to the occurrence of thresholds in chromium (VI) carcinogenesis."

NIOSH is currently assessing these studies and others to evaluate the reported dose-response relationships and to assess whether or not a threshold exists for CrVI exposure.

(5) Do short-term peak exposures play a role in causing adverse CrVI health effects? If so, what studies are available that examine these types of effects? How should short-term peak exposures be addressed when evaluating CrVI health effects data? In answering, please consider both animal and human studies.

Short-term peak exposures may be important in causing adverse CrVI health effects because they may overwhelm the reducing abilities and defense mechanisms of the body. ATSDR [2000] recently reviewed the adverse health effects of acute high concentration inhalation exposure in humans, including respiratory irritation, asthma, and gastrointestinal irritation. Langård and Nordhagen [1980] exposed rats to 40 mg/m^3 zinc chromate for 55 minutes. This study demonstrated the significance of CrVI ingestion and gastrointestinal absorption when animals are subjected to whole-body exposure at high concentrations. It is important to evaluate not only the mean or median exposure data, but also the peak exposure data, when analyzing CrVI health effects data.

6) How should OSHA address animal and epidemiological studies that rely on different analytical methods than are currently available to assess exposure when evaluating the health effects data contained in those studies?

Due to the large number of studies available over a long time period, many different analytical methods have been used and reported. The analytical methods reported vary in their sensitivity and specificity for CrVI compounds. Recent analytical methods are more sensitive than those used previously; the ability to speciate chromium has also improved over time. When assessing these studies it is important to evaluate the analytical methods used and critique how CrIII and CrVI levels, and soluble versus insoluble CrVI levels, were quantified. The exposure data reported in earlier studies may have a higher degree of uncertainty associated with them due to less sensitive analytical methods. When addressing studies that rely on different analytical methods, the potential shortcomings and uncertainties of the specific analytical methods used should be reported. The uncertainty of the exposure data in any particular study may be difficult to quantify but should be realized and discussed in any analysis.

(7) Animal studies are designed to test individual CrVI compounds (e.g., lead chromate, strontium chromate, potassium chromate). Epidemiological studies are designed to evaluate CrVI exposures in individual workplaces or by types of industries (e.g., chromate production, welding, pigment manufacture). Can or should the results from these individually tested compounds or work settings/industries be grouped together to assess the overall toxicity of CrVI or should each compound or industry be analyzed separately? Do different CrVI compounds have specific properties (e.g, solubility) that should be taken into consideration when evaluating animal or human studies?

Solubility is an important physical property of CrVI compounds which needs to be considered when analyzing animal or human study results. In the 1975 CrVI criteria document, NIOSH proposed different recommended exposure limits (RELs) for soluble versus insoluble CrVI compounds [NIOSH 1975]. At that time we stated that insoluble CrVI compounds were carcinogenic and soluble CrVI compounds were not. In our 1988 testimony to OSHA on the air contaminants standard, we indicated that, based on recent studies, all CrVI compounds should be considered carcinogenic [NIOSH 1988].

Each compound and industry should be analyzed individually when accurate and reproducible data are available. When study design and statistical power permit, separate analyses of specific chromium compounds should be performed. The results from the study of different compounds and industries should also be grouped together when possible to allow for the comparison of similar compounds or workplaces. One appropriate grouping would be to analyze the results of similar studies testing soluble or insoluble CrVI compounds. Other possible groupings include similar study designs, study populations, and industries.

The standardized designs and protocols of animal toxicity studies may allow for the comparison of the results of different studies. This may permit the analysis of the influence of compound variables such as solubility.

Epidemiologic studies have varying designs and reports that make direct comparisons of study results difficult. Paddle et al. [1997] indicated that meta-analysis of the chromium literature for any cancer other than lung cancer is not valid due to the heterogeneity of the studies. It also may be difficult in the epidemiologic studies to separate the effects of different compounds because of the high correlation between the exposures and other sources of variability, such as particle size distributions, reactivity and solubility.

It is difficult to generalize CrVI workplace exposures due to their great variability. However, it is important to be able to make general recommendations about working with CrVI compounds when dealing with exposures that are uncharacterized or involve a mixture of compounds. Conversely, having the results of individually tested compounds or industries allows recommendations to be made regarding a specific occupational exposure scenario when warranted.

B. Risk Assessment

OSHA is aware of the following risk assessments on human studies of lung cancer among workers exposed to CrVI via inhalation: The 1984 risk assessment prepared by the U.S. EPA (Ex. 19-1); the 1986 risk assessment prepared by Gibb et al. (Ex. 7-102); and the 1995 risk assessment by K.S. Crump Division (Ex. 13-5). These risk assessments relied heavily on the epidemiologic studies conducted by Mancuso (1975, Ex. 18-3) and Hayes et al. (Ex. 1979, Ex. 7-15). Since these risk assessments, Gibb et al. (2000, Ex. 25) has updated the investigation of the cohort originally studied by Hayes et al. (Ex. 7-15). This study notes limitations in the Mancuso data.

A further analysis for risk assessment of the Hayes cohort, as updated by Gibb et al. [2000b], has been prepared by NIOSH and is currently undergoing internal review. We will provide a copy of this analysis to OSHA when complete.

(8) Do the EPA (Ex. 19-1), the Gibb et al (Ex. 7-102) and the K.S. Crump (Ex. 13-5) risk assessments adequately characterize the lung cancer risks of CrVI? Please provide your rationale including information on studies selected and risk assessment methodology.

There were substantial limitations in the quality of the exposure information available in the Mancuso [1975] study, which introduced uncertainty into the noted risk assessments performed by EPA, Gibb et al., and Crump using this data. We believe that the new study performed by Gibb et al. [2000b] provides the best currently

available data for risk assessment purposes, and that the NIOSH analysis of this data noted above will provide the most reliable information on risks to workers.

(9) What approaches (i.e., methods, models, data used) should OSHA use for estimating risk of CrVI exposure?

As stated above, we believe that the data from the recent paper by Gibb et al. [2000b] provide the best basis for a risk assessment. It would be useful, however, to compare the risk estimates derived from analysis of this study to those derived from the studies by Mancuso [1975]. A high degree of concordance on estimates of lifetime risk from the different studies would add greater confidence to the risk estimation. We would recommend using statistical models appropriate for epidemiologic data (i.e., either Poisson regression or the Cox Proportional Hazards model) as the underlying methodology for the risk assessment.

(10) Are there biological endpoints, besides lung cancer, that could or should be used to estimate the occupational risk to CrVI-exposed workers?

There is an indication of possible excess heart disease in a chromium exposed cohort that, to our knowledge, has not been reported elsewhere. Gibb et al. [2000b] observed a statistically significant overall excess in heart disease mortality (SMR=1.14, 95%CI=1.01-1.29). For nonwhites, it was higher (SMR=1.32, 95%CI=1.05-1.63), which is particularly striking because exposures were higher in nonwhites (primarily black men), and the healthy worker effect is generally stronger in black men. The true excess could be considerably higher and was based on a mean employment duration of only 3.7 yrs. The heart disease mortality experience of the Mancuso cohort does not appear to have been examined. Heart disease is a biologically plausible consequence of hexavalent chromium exposure because lipid peroxidation is an hypothesized mechanism of atherosclerosis [Witzum and Steinberg 1991], and oxidative stress is a known consequence of chromium exposure and has been postulated for its carcinogenicity [Leonard et al. 2000]. However, this observation needs to be duplicated in other populations and possible smoking confounding assessed.

In addition, at high exposures the irritant effects on the skin and nasal mucosa are well known and could be used to estimate risk.

(11) What mathematical models are appropriate to quantify the risk of cancer or other adverse health effects associated with exposure to CrVI? What are the strengths and weaknesses of those models?

A linear exposure-response is generally the default relationship expected for carcinogenic effects. However, OSHA may want to examine non-linear models to determine whether the assumption of a linear model is adequate, especially for non-cancer outcomes. The strength of a statistical model, for example a linear model, is its

ability to succinctly summarize relationships between exposure history and subsequent health outcomes. However, a statistical model may not accurately reflect the underlying relationship between exposure and health effect. In this situation, one weakness of a statistical model may be that the model cannot be ruled out due to insufficient statistical power.

(14) What other factors should OSHA take into consideration when analyzing risks associated with exposure to CrVI at the current permissible exposure level and in determining safe levels of exposure to CrVI?

The adequacy of retrospective exposure assessment and misclassification issues are important factors in estimating exposure-response. To the extent possible, OSHA should consider the impact of these errors on the risk assessment. OSHA should also consider the following questions:

- Is there any evidence for a threshold?
- Is cumulative exposure or average exposure the most important predictor of risk?
- Is there evidence for a dose-rate effect?
- Is the risk modified by other exposures or personal characteristics?

C. Methods of Analyzing Exposure Levels

(15) Are there methods other than ID-215 for measuring exposure levels in the range of 0.02 to 10 ug/m^3 that would be as accurate as, or more accurate than, OSHA's ID-215?

A new NIOSH procedure, Method No. 7605, "Hexavalent Chromium by Ion Chromatography," will be published in the *NIOSH Manual of Analytical Methods* [NIOSH 2002 Draft a]. This method gives equivalent performance to OSHA ID-215 over the range cited [Boiano et al. 2000]. Also, a new ASTM method for hexavalent chromium in workplace air, "Standard Test Method for the Determination of Hexavalent Chromium in Workplace Air by Ion Chromatography and Spectrophotometric Measurement using 1,5-Diphenylcarbazide," has been approved and will be published in 2003 [ASTM 2002]. An ISO procedure for the measurement of CrVI in workplace air is under development and will be circulated in early 2003 as a draft international standard. ISO documents are copyrighted, so a copy of the draft method cannot accompany this response.

(16) Are there methods for conducting wipe samples?

The American Society for Testing Materials has developed ASTM E1728, "Standard Practice for the Collection of Lead in Surface Dust Using Wipe Sampling Techniques." (NIOSH cannot provide a copy of this standard because it is copyrighted by ASTM

International). While the ASTM dust wipe procedure is described for subsequent lead determination, the same sampling procedure is applicable to the collection of CrVI in surface dust. Sample preparation and analysis procedures to be followed would be similar to those described in the methods referenced in the response to Question #15 above.

(17) Are there methods for conducting field-tests?

NIOSH and US Air Force researchers have developed and evaluated a field method for the determination of CrVI in workplace air samples [Wang et al. 1999]. A new NIOSH procedure, Method No. 7703, "Hexavalent Chromium by Portable Spectrophotometry," will be published in the *NIOSH Manual of Analytical Methods* [NIOSH 2002 Draft b]. This method gives equivalent performance to OSHA ID-215 over the range cited.

(18) Are there methods to determine the presence or absence of CrVI in buildings for which no blueprints are in existence?

Spot test methods are available for making immediate decisions in the field about the presence of CrVI in coatings such as paint. However, spot test procedures require thorough validation using statistically sound testing and performance criteria before being used for screening [Song et al. 2001].

D. OSHA's Investigations into Occupational Exposures, Control Measures, and Technological and Economic Feasibility

As noted by OSHA on pp. 54391-2 of the FR notice, NIOSH entered into an Interagency Agreement (IAG) [CDC-NIOSH/OSHA IAG 98-16, Control Technology Assessment for CrVI] with OSHA's Office of Regulatory Analysis to conduct industrial hygiene surveys to quantitatively characterize occupational exposures to CrVI and to document engineering controls and work practices in affected industries. NIOSH continues to deliver the industrial hygiene reports to OSHA as they are completed. These reports include data on employee exposure and monitoring, control measures and technological feasibility, personal protective equipment, and some aspects of economic impact. To date, we have forwarded the following completed letter-reports to OSHA:

Facility	Number	Industrial Sector/Operation
1	9052	Chromium electroplating
2	9053	Painting (chromate paints
3	9054	Printing-ink manufacturing
4	9055	Chromium-sulfate manufacturing

5	9056	Refractory-brick manufacturing
6	9057	Colored-glass manufacturing
7	9058	Painting
8	9059	Printing
9	9060	Welding
10	9061	Portland-cement products manufacturing
11	9062	Woodworking (CCA-treated wood)
14	9065	Welding
17	9068	Chromate-paint removal (blasting) (construction)

F. Employee Training

(39) How do you determine the effectiveness of the training? Are decreased absenteeism, decreased medical/insurance costs, decreased accident rates/severity, and increased productivity factors in your determination? Are there any other factors in your determination? How are language barriers to training addressed?

To identify the elements of training that are critical to increased effectiveness, NIOSH has developed a research guide known as the training intervention effectiveness research model (TIER model) [NIOSH 1999]. The TIER model provides a logical framework for the planning and implementation of evaluations of training effectiveness. The model differentiates between immediate outcomes of training and later-changing impacts of training. Immediate outcomes of training can include changes in participants' knowledge, attitudes, behavioral intent, and demonstrated skills or abilities, as well as participant satisfaction with the training. Later-changing impacts of training can include longer-term retention of knowledge, attitudes, behavioral intents, abilities, and skills by the training participants; application of learned information or skills in the workplace; changes in work practices; and improvements in workplace health (decreased absenteeism and accident rates/severity) and economic indicators (medical insurance costs, productivity levels) that could reflect application of the training to normal operating procedures.

Information collected in the evaluations of training effectiveness can be used in making future improvements in the training. The TIER model is structured so that improvements in training can be made based on examination of the outcomes from previous training. This approach complements OSHA's informational booklet *Training Requirements in OSHA Standards and Training Guidelines* that encourages ongoing

revision and improvement in training based on the feedback received from previously conducted training [OSHA 1998].

Language barriers in training should be addressed by providing training that can effectively communicate the information to the employees. This might include multi-lingual written training materials, provision of interpreters, and/or provision of graphic or auditory training information aimed for low literacy levels. Outcome and impact data may be useful in determining whether language barriers exist.

(40) Are there ways in which CrVI-related training could be improved?

Employer-specific improvements in CrVI-related training can be made based on outcomes and feedback that were received from previously conducted training. Training efforts can target high risk-employees who represent occupations or populations associated with increased rates of occupational injury. Content of Federal or State OSHA standards applicable to specified occupations can provide guidance in selecting the content included in the training. Job hazard analyses facilitate identification of tasks performed in a specific job, thus identifying hazards and revealing alternative safer work practices that may also provide information to improve training.

Collecting job-related information on where and how illnesses and injuries occur can also provide an employer with modifications in training that can be made to address potentially hazardous areas. Sources of information include the following:

- examination of employer accident and injury records
- observations of employee work performances
- collection of employee feedback regarding near-miss injuries or work areas that are seen as unsafe
- examination of alerts provided by safety and health organizations for job tasks found to be unsafe

G. Medical Programs

(41) What medical or clinical examinations have potential usefulness in identifying workers with adverse health effects resulting from occupational CrVI exposure? Include specific tests or procedures used in any such examination and other useful information, such as the types of laboratories used for biological tests, the frequency of examinations and follow-up tests, and the contents of the examinations?

Medical monitoring of CrVI-exposed workers should include a pre-placement and annual physical examination, including a comprehensive work history questionnaire, smoking history, and comprehensive physical examination with an emphasis on the respiratory and integumentary systems [Barceloux DG 1999; Miksche and Lewalter

1997]. Laboratory tests should be conducted as deemed appropriate by the attending health care professional, including urinalysis, chest radiograph, and kidney function tests. More frequent examinations and more extensive testing may be indicated in workers who display adverse effects of CrVI occupational exposure.

We have found no other tests that have definitive utility although several have been suggested by more than one source for the purposes of surveillance:

- Cytological nasal examination by brushing of the nasal mucosa has been suggested as a means of surveillance for cellular atypia and premalignant cells of the upper respiratory tract [Bolla et al. 1990; Langård 2001].

- Skin patch testing may be a means of identifying workers who may subsequently develop occupational asthma in response to chromium exposure. Positive skin patch test results have been identified prior to the onset of asthmatic symptoms [Langård 2001].

- Monitoring for the presence of Low Molecular Weight (LMW) proteins in the urine may help identify early renal toxicity, although, as a surveillance modality, screening for the presence of LMW proteins is neither entirely sensitive nor specific [Langård 2001; Ryan et al. 2000].

- Routine sputum cytology may help identify early lung cancer in asymptomatic individuals. Performance of this test is costly and, unless performed correctly, has low sensitivity for the presence of malignant cells [Ryan et al. 2000].

(44) Are there any studies that suggest that elevated biological indicators (such as CrVI in blood or urine) are associated with an elevated risk of lung cancer or other adverse health effects such as asthma? What are normal levels of chromium in blood or urine in non-occupational exposed populations? Are these indicators affected by diet?

Values reported by the World Health Organization (WHO) that are based on U.S. Environmental Protection Agency (EPA) data range from 0.02 to 7 µg/100 ml in serum and plasma and 0.5 to 5.4 µg /100 ml in RBCs of non-occupationally exposed populations. Chromium concentrations in urine of non-occupationally exposed persons measured by GF-AAS are less than 1 µg/L. Dietary exposures (largely CrIII) and environmental exposures such as tobacco smoke affect the measured levels of chromium [Geller 2001; World Health Organization 1996; Lauwerys and Hoet 2001].

(45) Is there any information that suggests that biological indicators other than CrVI in blood or urine could be appropriate for evaluating risk of adverse health effects associated with CrVI exposures among workers?

Chromium is primarily excreted in the urine via the kidneys (~60%), with some additional excretion in the bile, feces, sweat, hair and nails, and breast milk [World Health Organization 1996; Ryan et al. 2000]. Attempts at monitoring for exposure to

chromium by sampling hair and lung tissue have been unsuccessful Langård [2001]. Chromium concentrations measured in the seminal fluid of some groups of stainless steel workers were found to be markedly elevated [Langård 2001].

The measurement of chromium in the urine and the blood appears to be the most appropriate testing for evaluating exposures to CrVI exposures in workers [Lauwerys and Hoet 2001]. However, the relationship between an individual worker's level of exposure and the risk of specific adverse health events associated with that exposure appears to be less clearly defined.

(46) Are there any studies that suggest that chromium with other valences, other than in the CrVI valence, can be taken up by the red blood cells?

Only hexavalent chromium is capable of crossing cell membranes; CrIII is unable to cross the cell membrane [Geller 2001; World Health Organization 1996; Lauwerys and Hoet 2001; Ryan et al. 2000; Miksche and Lewalter 1997]. Once CrVI crosses the red blood cell membrane, it is rapidly reduced to trivalent chromium which binds essentially irreversibly to intracellular proteins including hemoglobin.

Both within the lungs and the gastrointestinal tract, CrVI is reduced to CrIII; this inherent mechanism serves to minimize the absorption of the chromium [Geller 2001; Ryan et al. 2000; World Health Organization 1996; Langård 2001]. Exposures to CrVI that overwhelm this mechanism can result in absorption of CrVI. Extracellular glutathione acts to reduce CrVI to CrIII, thereby decreasing the burden of CrVI available to cross cell membranes, bind to intracellular proteins, and cause DNA damage [Geller 2001].

Measurement of chromium within RBCs (CrVI that has been reduced to CrIII), therefore, provides a qualitative assessment that the body's inherent detoxification mechanisms have been exceeded [Geller 2001; World Health Organization 1996].

(47) When you evaluate an employee's chromium-blood levels, do you use whole blood or packed red blood cells? What is the significance of using one over the other?

Chromium-blood levels in packed red blood cells reflect hexavalent chromium exposure only. Once bound to the intracellular material of the red blood cell, the chromium persists for the life of the cell [World Health Organization 1996; Lauwerys and Hoet 2001; Ryan et al. 2000]. Measuring the concentration of chromium within the red blood cell can serve, therefore, as a marker for internal doses of CrVI compounds [World Health Organization 1996]. Measurement of chromium in whole blood can be used for exposure screening, but it is not as useful as plasma, urine or RBCs. These other biological media have been more extensively studied and determined to be better indicators of chromium exposure [Ryan et al. 2000]. The measurement of chromium concentrations in plasma has great diagnostic sensitivity for assessing recent exposure [Lauwerys and Hoet 2001; Ryan et al. 2000].

Because hexavalent chromium is rapidly reduced by the body as a detoxification mechanism, it is trivalent chromium that is measured in the urine and in the plasma. [Miksche and Lewalter 1997]. It is therefore important to consider that the measured levels of chromium, whether in the urine or in the plasma, do not readily distinguish between the forms of chromium to which a person is exposed. Chromium in the plasma portion of the blood represents both absorbed CrIII and reduced CrVI.

Chromium within the red blood cells is a more accurate reflection of exposure to CrVI as this is the only form of the metal that is capable of crossing cell membranes. One study has shown, however, that the concentration of chromium within the red cell depends upon inherent genetic polymorphisms. Spontaneous plasma reduction capacity (SPRC) determines the ability of an individual to reduce CrVI to CrIII; once converted to CrIII, chromium can no longer enter into the red blood cell. Persons with "strong" SPRC therefore will excrete a relatively higher concentration of chromium in the urine and have lower concentrations of chromium within the red blood cells. Conversely, "weak" reducers, given exposures to comparable environmental levels of hexavalent chromium, will show the opposite, i.e., lower concentrations of chromium in the urine and higher concentrations within the red blood cells [Miksche and Lewalter 1997; World Health Organization 1996; Geller 2001].

Measurement of chromium in both the urine and in the red blood cells also permits a determination to be made as to the time course of exposure to this metal. Chromium bound within red blood cells remains so for the life of the cell, approximately 120 days. The presence of chromium in red blood cells therefore indicates an exposure to CrVI at any point during the life of the cell. By contrast, chromium concentrations measured in the urine reflect more recent exposure to either detoxified hexavalent or nontoxic trivalent chromium metal [Miksche and Lewalter 1997; Langård 2001; Ryan et al. 2000].

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