TOXICOLOGICAL APPROACH TO SETTING SPACECRAFT MAXIMUM ALLOWABLE CONCENTRATIONS FOR CARBON MONOXIDE

K.L. Wong*, T.F. Limero*, and J.T. James.
NASA-JSC Biomedical Operations and Research Branch,
Johnson Space Center, Houston, Texas.
*Krug Life Sciences, Houston, Texas.

ABSTRACT

The Spacecraft Maximum Allowable Concentrations (SMACs) are exposure limits for airborne chemicals used by the National Space and Aeronautics Administration (NASA) in spacecraft. The aim of these SMACs is to protect the spacecraft crew against adverse health effects and performanace decrements that would interfere with mission objectives. Because the 1-hr and 24-hr SMACs are set for contingencies, minor, reversible toxic effects that do not affect mission objectives are acceptable. The 7-day, 30-day, or 180-day SMACs are aimed at nominal operations, so they are established at levels that would not cause noncarcinogenic toxic effects and more than one case of tumor per 1000 exposed individuals over the background. The process used to set the SMACs for carbon monoxide (CO) is described to illustrate the approach used by NASA.

After the toxicological literature on CO was reviewed, the data were summarized and separated into acute, subchronic, and chronic toxicity data. CO's toxicity depends on the formation of carboxyhemoglobin (COHb) in the blood, reducing the blood's oxygen-carrying capacity. The initial task was to estimate the COHb levels that would not produce toxic effects in the brain and heart. Then the Coburn-Forster-Kane (CFK) equation was used to calculate the CO exposure concentration that would lead to a no-effect COHb level upon exposure for a given duration (1 hour to 180 days) and that CO concentration was selected as the SMAC. The 1-hr and 24-hr SMACs were set at 55 ppm and 20 ppm, respectively, to prevent central nervous system (CNS) impairment at COHb of 3%. Ten ppm was selected to be the 7-day, 30-day, and 180-day SMACs to ensure that the COHb level would not exceed 1.6%, which would protect against abnormal heart rhythms and CNS impairment.

1. INTRODUCTION

Inhalation exposures to some chemicals may lead to toxic effects that impair the health or performance of the exposed subjects. To provide a safe environment for the astronauts in spacecraft, NASA has established SMACs for 190 chemicals[1]. The SMACs are exposure limits that, if not exceeded, would prevent health injuries and the crew's performance decrement due to exposures to airborne chemicals. The official SMACs were set, without documentation, about 20 years ago and currently they are designated as 7-day SMACs for space shuttle missions.

There are two reasons why the official 7-day SMACs need to be revised: 1) availability of new toxicity data for most of these chemicals and 2) scientists have a better understanding of toxicologic principles. In addition to revision of the 7-day SMACs, a range of SMACs is necessary to a adequately cover all potential exposures associated with nominal operations, contingency events and extended duration missions. The Johnson Space Center (JSC) Toxicology Group has decided that this range should include SMACs for 1 hr, 24 hr, 30 days, and 180 days. The 7-day, 30-day, and 180-day SMACs are designed for nominal operations, so they are set at levels that would not cause noncarcinogenic toxic effects. For carcinogens, the 7-day, 30-day, and 180-day SMACs are established so that the risk of getting tumors is no more than one in a thousand above the background level. In contrast, the 1-hr and 24-hr SMACs are aimed at contingency situations. Therefore, minor, reversible toxic effects are acceptable provided that they do not prevent the spacecraft crew from achieving the mission objectives. Examples of these acceptable toxic effects are mild mucosal irritation and headaches. Compared with the longer-term SMACs, the 1-hr and 24-hr SMACs are, therefore, sometimes set at levels relatively higher than what the differences in exposure duration would suggest.

The JSC Toxicology Group has embarked on the project of setting new 1-hr, 24-hr, 7-day, 30-day, and 180-day SMACs for the 190 chemicals in the current official list and a number of new chemicals. The new SMACs will be used in support of the Space Shuttle missions and future Space Station Freedom missions. In addition, some of the new SMACs will serve as the design criteria for the air revitalization subsystem of the Environment Control and Life Support System and for air-quality monitoring equipment of the Environmental Health System in the Space Station Freedom. Overly conservative SMACs must be avoided because these could cause these systems to be designed with unnecessary weight or power

burden.

Establishing new SMACs proceeds in three stages. First, the JSC Toxicology Group sets interim SMACs based on its understanding of the chemical toxicity and state-of-the-art toxicologic principles, assisted by a guideline provided by the National Research Council's Committee on Toxicology (NRC-COT). The interim SMACs and their rationale are, then, reviewed by the NRC-COT. Finally, the JSC Toxicology Group would, if necessary, revise the interim SMAC values and the documentation according to the NRC-COT's comments. The interim SMACs become official after this review process.

This paper describes the JSC Toxicology Group's approach in setting the new SMACs by using carbon monoxide as an example. CO is a colorless and odorless gas[2]. It is produced both endogenously and exogenously. In the body, CO is produced at a rate of 0.4 ml/hr via catabolism of hemoglobin and nonhemoglobin heme[3]. The incomplete oxidation during thermodegradation of materials containing carbon in an atmosphere containing oxygen is an exogenous source of CO. For instance, CO could be produced when gas stoves and furnaces are in use. Smoking is another common indoor exogenous source of CO[4], which has been measured in main-stream cigarette smoke at 40,000-50,000 ppm[5]. The primary outdoor source of CO is automobile exhaust[4]. In the 1960's and 1970's, CO concentrations of 20-30 ppm were commonly detected on expressways in major U.S. cities and on a busy street inside London during rush hours, with peak concentrations exceeding 100-300 ppm[4,5].

Inside spacecraft, there is no known use of carbon monoxide. However, CO metabolically produced by the astronauts may accumulate in the cabin. Of course, a large amount of carbon monoxide may be produced if there were a thermodegradation accident in the cabin. Therefore, carbon monoxide could be a threat to the crew's health and SMACs for carbon monoxide are critically needed for crew protection.

2. GENERAL APPROACH IN SETTING SMACs

2.1. Literature Searches

2.1.1. Nonbiological Literature

The SMAC-setting process begins with a literature search on the important physical and chemical properties of the chemical. Information gathered typically includes the Chemical Abstract registry number, chemical structure, molecular weight, boiling point, melting point, and vapor pressure. The Chemical Abstract registry number is to facilitate the toxicological literature search. The chemical structure sometimes gives a preliminary idea of the chemical's toxicity and it, thus, also helps to plan the toxicological literature search. The molecular weight is used in the conversion of airborne concentration units from mg/m^3 to ppm or vice versa.

The boiling and melting points determine the potential physical form of the chemical in the spacecraft. The physical form, in turn, determines the exposure pathway. For instance, if the chemical exists as a solid, the potential exposure routes are ingestion, cutaneous contact, and inhalation as a dust. Since ingestion can be avoided if care is exercised by the astronauts and cutaneous contacts with a solid usually will not present a systemic toxic hazard, the most significant exposure route of a solid is by inhalation, provided that the solid exists as particulate. On the other hand, if the chemical is a liquid at room temperature and normal ambient pressure, it may be inhaled as a vapor, plus there may be cutaneous exposures. Of course, if the chemical exists as a gas, inhalation would be the primary route of exposure.

The vapor pressure gives an indication of the potential for the chemical to be inhaled. For example, if the vapor pressure is low, the liquid may have to be aerosolized before it would present a significant inhalation hazard. However, if the liquid is highly volatile, inhalation in the vapor form would be the most likely scenario. Although solid or liquid chemicals will float in air in microgravity, presenting a potential to be ingested, the chance of such an event occurring to a significant extend is very slim. Consequently, oral exposures are not considered in setting SMACs.

2.1.2. Biological Literature

The second step is to thoroughly search the literature on the toxicological properties of the chemical, using the computerized data bases of the National Library of Medicine. The particular data bases routinely searched are the TOXLINE, TOXLIT, IRIS, and the Hazardous Substances Data Bank. Occasionally, Chemical Abstracts is also searched. After an initial screen of the publication titles, publications of interest are selected and their abstracts are then extracted from the data bases. These abstracts are read and the key publications are obtained via our library.

2.1.3. Literature Selection Criteria

The selection criteria for publications include the type of study system used by the investigators, the species of the study subjects, and the exposure route used in the study. These criteria all could influence the usefulness of the publication in setting SMACs.

2.1.3.1. Study System as a Selection Criterion

Except for the studies of the effect of the chemical on genetic materials, the literature on the chemical's effect on an in vitro system is routinely not reviewed. In vitro systems are systems in which the experiments are conducted with tissues or cells isolated from the body and maintained in a growth media in a petri dish or flask. The reason in vitro studies are not relied upon is three-fold. First, not all the cell types are present in an in vitro system, so the response seen in the system may be different from the response seen in the body. Second, when

the tissues or cells are maintained in a growth media, the tissues or cells may change their biological characteristics so that they react to the chemical differently than they would have in the body. Third, it is difficult to convert the chemical concentration used in the growth media to an inhalation exposure concentration. Due to the artificial nature and all the uncertainties on the representativeness of the results, in vitro data play a very small role in setting SMACs.

2.1.3.2. Species as a Selection Criterion

Publications dealing with the toxic effects on plants and nonmammalian animals are usually ignored because the meaning of a toxic effect in plants or nonmammalian animals is doubtful for astronauts, the subjects protected by the SMACs.

2.1.3.3. Exposure Route as a Selection Criterion

In terms of the exposure route, there is little emphasis on studies done using oral or cutaneuous routes or studies in which the chemical was administered into the experimental subject by injection. This approach is taken because, to estimate a safe exposure limit for an airborne chemical, the toxic effects by inhalation exposures are most relevant. Although there are ways to estimate the equivalent inhalation exposure concentrations for exposures by noninhalation routes, there are controversies on the accuracy of the methods. Some toxicologists even take the position that extrapolation of toxicological data from a noninhalation route of exposure to inhalation is invalid. However, if there is no toxicity information on a chemical given by inhalation and a "safe" airborne exposure limit is definitely needed, then sometimes we may calculate an inhalation exposure concentration that is somewhat equivalent to a dose of the chemical given by injection or oral administration. The calculation assumes that the chemical is absorbed to the same degree regardless whether the exposure is by an oral or inhalation route and that the absorption rate stays constant during the entire duration of an inhalation exposure. The equivalent inhalation exposure concentration is calculated using the typical minute volume of an average adult. Even though these assumptions may not be precisely correct, they tend to err on the conservative side, so the extrapolation method is considered an acceptable means of calculating the equivalent inhalation exposure concentration as a last resort.

2.1.4. Other Types of Information Gathered

In addition to reviewing the literature on the toxicity of the chemical, the literature on the absorption, metabolism (how the body modifies the chemical), excretion, pharmacokinetics (how fast the body handles the chemical), and mechanism of toxicity (how the chemical causes toxic effects in the body) is scrutinized. Such data are important in setting the SMACs, but they are typically incomplete.

Absorption and excretion information is useful. Knowing how well the body takes in the chemical and how well it eliminates the chemical provides a better understanding of the biological fate of the chemical, which in turn helps in the interpretation of the toxicity data.

Metabolism information is important because some chemicals are toxic after the body converts the chemicals into metabolites which are more toxicologically active than the parent chemicals. For these chemicals, the SMACs should be set according to the potential level of the active metabolite in the body and not according to that of the parent chemical.

Knowing the pharmacokinetics of the chemical could provide us a way to estimate the level of the chemical at the target site in the body at different times during or after an inhalation exposure. Because the toxicity depends on the chemical level at the target site, the estimates of that level with time allows the proper adjustments of toxicity data from a certain exposure duration in a study to the duration for which the SMAC is designed.

2.2. Evaluation of the Toxicological Literature

Evaluation of the information on toxicity, metabolism, pharmacokinetics, excretion, and mechanism of toxicity provides a thorough understanding of the toxic nature of the chemical in the biological system. They are of value in making predictions on the nontoxic exposure concentrations for different exposure durations.

2.2.1. Species

Because a chemical's toxicity, metabolism, pharmacokinetics, excretion, and mechanism of toxicity could vary depending on the species of the exposed subject, it is important that SMACs should be set relying on data gathered from human subjects whenever possible. Therefore, in evaluating the toxicological literature, emphasis is placed on human studies. Due to ethical reasons, many types of toxicological studies are not conducted on human subjects. As a result, we sometimes have to rely on toxicological data gathered in studies using laboratory animals. Among the data gathered from laboratory animals, more weight is given to data in nonhuman primates because of the physiological and anatomical similarities of monkeys, baboons, etc., to man. For data gathered in nonprimate animal species, a slight preference is given to larger animal species, e.g., the dog, than rodents. The reason is that the human physiology and anatomy are more analogous to that in larger species.

2.2.2. Exposure Duration

Because the pattern of toxicity of a chemical could vary with the exposure duration, the toxicity data are categorized into acute, subchronic, and chronic. Acute toxic changes are adverse effects produced by the chemical after a single, short-term exposure. Adverse effects on the body caused by the chemical after an exposure lasting almost a normal life span

are termed chronic toxic changes. Subchronic toxicity is the toxic effect produced by a chemical exposure that lasts between a short-term exposure and a near life-time exposure. Actually, the transition from acute toxicity to subchronic toxicity sometimes is imprecise because the definition of subchronic toxicity is not very specific. Therefore, some toxicologists have added a quantitative criterion into the definition. They define subchronic toxicity as the toxic effect seen after the subject has been exposed to the chemical for less than a life time, but more than 10% of the life time. Because 10% of a life span of 70 year is too long a time relative to the exposure durations of the SMACs, here we have chosen the less specific definition of subchronic toxicity. We have opted for a definition that any exposure lasting for about a week to almost a life time is subchronic.

Because the toxicity of a chemical could differ according to the exposure duration, the categorization of the toxicity information found in the literature into acute, subchronic, and chronic types is important for the setting of SMACs of different duration. Ideally, a SMAC should be set using toxicological data generated in a study in which the exposure duration was similar to the exposure duration that the SMAC is intended to be used. So the 1-hr and 24-hr SMACs should be set using acute toxicological data. By the same token, subchronic toxicological data should be used to establish the 7-day, 30-day, and 180-day SMACs.

Chronic toxicological data usually yield information on the carcinogenicity of the chemicals. Tumors are thought to be produced via a different process than the production of noncarcinogenic endpoints, e.g., liver injury. The setting of SMACs based on the carcinogenesis of a chemical, consequently, involves a different approach than the setting of SMACs based on noncarcinogenic endpoint. Such an approach will be described separately below.

2.2.3. Data Quality

To make the SMACs meaningful, it is obvious that the SMACs should be established based on good quality data. In evaluating the literature, attention is always placed on the data quality. The factors considered in assessing the data quality are the number of test subjects, the homogeneity of test subjects, the way the exposure concentration was determined in the study, the purity of the chemical used, the method of detecting the toxic changes, and the way study results were analyzed.

2.2.3.1. Number of Test Subjects

The study has to use a sufficient number of test subjects in order to make the response detected in the study representative of what would be seen in a population. The sample size is important because, unlike physical or chemical systems, biological systems could have quite a large degree of variability due to differences in the genetic makeup. If the data were gathered in a study with only a few human subjects, the average response in these subjects most probably would not be predictive of how other human beings, such as astronauts, would react to the chemical. As a result, SMACs set on the results of such a study are of doubtful value.

2.2.3.2. Homogeneity of Test Subjects

While the homogeneity of the test subjects used would not, by itself, eliminate a study from being relied upon in setting SMACs, it is still an important criterion. Because a test subject's response to a chemical is influenced by many factors related to the subject, it is important that the study subjects are very similar anatomically and physiologically so that any changes seen in the study could be ascribed to the chemical exposure alone. Therefore, we prefer studies in which the composition of the exposed group is very similar to that of the control (nonexposed) group. Confounding factors, such as existing disease state and smoking habit, that may influence the response to the chemical, should be eliminated to the extent possible. Given the impossibility of conducting a study with a perfectly homogeneous human population, these confounding factors should be randomized evenly between the exposed and the nonexposed group. In laboratory animal studies, the control of confounding factors is easier. So among animal studies, an emphasis should be placed on studies with healthy animals of similar age and body weight.

2.2.3.3. Measurement of Exposure Concentrations

Since the SMACs are set based on the toxic effects detected at some specific exposure concentrations in studies in the literature, it is important that the reported exposure concentrations were accurate. Consequently, during the literature evaluation, attention is paid to the concentration measurement method. Questions usually asked include whether the exposure concentration was measured analytically or estimated from the amount of chemical introduced into the exposure system. If the concentration was measured analytically, we would determine if the analytical method is specific for the chemical and if it is sensitive enough in the range of the study concentrations.

2.2.3.4. Chemical Purity

An issue related to the method of determining the exposure concentration is the purity of the chemical used in the study. To eliminate exposures to chemicals other than the study chemical as a confounding factor, preference is given to studies in which the subjects were exposed to only one chemical. That means in experimental studies, the study chemical used should be of high purity (over 99% preferably and at least 95%). Attention should be paid to the identities and relative quantities of the impurities. In epidemiological or occupational studies, it is difficult to control the exposure, so there is no exact purity requirement. For this reason, experimental human studies are preferred over epidemiological or occupational studies.

2.2.3.5. Detection Method of the Toxic Effect

Another important evaluation criterion is the method used to detect the toxic effect. Other than studies investigating chemical-induced headache and mucosal irritation, objective methods are given more weight than subjective methods to avoid biases of the investigators. If the study involves human subjects, it is prefered that the subjects did not know whether they were being exposed to the chemical or just air. If the method of detecting the toxic effect involves the investigators' judgment, a double blinded study is prefered. Other factors considered include whether the method is specific for the toxic effect to be detected, the method's sensitivity and accuracy, and the reproducibility of the method. It is obvious that the specifity and accuracy of the endpoint detection method are important because the measured change should reflect the real toxic effect. By the same token, any lack of measurable changes should represent a real absence of toxic effect, so the detection method must be sensitive. Finally, the method's reproducibility is important in ascertaining that the measured change was caused by the chemical and not due to any aberrant behavior of the detection method.

2.2.3.6. Data Evaluation in the Study

To ensure that the investigators drew the correct conclusion in the study, it is important that the data were analyzed properly. To deal with biological data that could vary tremendously, the use of statistics is imperative. We routinely check whether the toxic changes reported were based on suitable statistical analyses.

3. SMAC Setting Procedure

The general procedure is to set a maximum allowable concentration (MAC) for each toxic endpoint meaningful for the exposure duration of interest and select the lowest MAC, among those of different endpoints, as the SMAC for that duration. The way to set a MAC for carcinogenesis is different from that for noncarcinogenic endpoints. The ways for setting the two types of MACs are described separately.

3.1. MAC based on noncarcinogenic endpoint

The SMAC for an exposure duration is defined as the maximum exposure concentration that causes no or practically no toxicity for that exposure duration. The MAC for a particular toxic endpoint is, then, the maximum exposure concentration that would not cause that toxic effect. It is believed that the higher the exposure concentration the greater the toxicity. So, from the study results, we are interested in the maximum exposure concentration that failed to produce a specific toxic effect to a practical extent and such a concentration is called a no-observed-adverse-effect-level or NOAEL. To obtain the NOAEL for a noncarcinogenic endpoint, the acute, subchronic, and chronic toxicity data are separated. In each of these three categories, the data are further separated according to the toxic endpoint. The highest exposure concentration known not to cause a particular noncarcinogenic toxic effect is identified as the NOAEL for that effect.

3.1.1. Safety Factors

Due to uncertainties inherent in some studies, to err on the conservative side, the NOAEL for a particular noncarcinogenic endpoint is sometimes divided by safety factors to arrive at the MAC. If the study used animals as the test subjects, an interspecies extrapolation factor may be used. If the study was of an exposure duration different from the exposure duration of the SMAC, a time-adjustment factor is applied. The time-adjustment factor is based on the Haber's rule that the product of the exposure concentration and exposure time is approximately constant. It should be pointed out that the Haber's rule is not universally applicable.

Another situation in which a safety factor is applied is when the chemical's toxic effect is similar to a biological effect induced by microgravity. For instance, microgravity has been known to reduce the red blood cell mass and to cause minor irregular heart rhythm in astronauts during a mission[7,8]. If a chemical also produces a change in the red blood cell or heart rhythm, a microgravity-related safety factor is usually applied on the NOAEL to derive the MAC.

3.2. MAC based on carcinogenesis

Most carcinogens have been shown to act by damaging the genetic material of the body and these are called genotoxic carcinogens. Because there is a better understanding of genotoxic carcinogens, the setting of MAC based on carcinogenesis is described using genotoxic carcinogens as examples. The current thought is that there is no such thing as a NOAEL for the tumor response to genotoxic carcinogens. That means even a single molecule of genotoxic carcinogen in the body could theoretically lead to tumor development. The JSC Toxicology Group has adopted 1/1000 as an acceptable tumor risk. So the maximum concentration of a carcinogen that could produce one case of tumor, in excess of the background, in 1000 exposed individuals is the MAC for that carcinogen.

The MAC based on carcinogenesis is usually generated from chronic test data in laboratory animals. Using these data, the U.S. Environmental Protection Agency or the NRC-COT calculated, with the linearized multistage model, the upper 95% confidence limit of the life-time exposure concentration that yields an excess tumor risk of 1/1000. We obtain the MAC based on carcinogenesis by taking that upper confidence limit and adjust, with the method of Crump and Howe[9], for the difference in exposure duration between the continuous, life-time exposure of the EPA or NRC-COT value and the exposure duration for which the SMAC is designed.

4. Setting the SMACs for Carbon Monoxide

The setting of the carbon monoxide's SMACs will be used to illustrate the procedure of establishing SMACs described above.

4.1. General Biological Information on CO

Carbon monoxide is absorbed rapidly in the lung at a rate of about 25.8 ml /min x mm Hg[10]. Carbon monoxide's elimination half-life is 4-5 hours in resting subjects when breathing ambient air[4].
As mentioned earlier, an understanding of the mechanism of toxicity is very useful in setting SMACs. Information on the mechanism of toxicity of carbon monoxide indicates that, unlike most chemicals, the exposure concentration of carbon monoxide together with the exposure duration is not the best way to characterize carbon monoxide's toxic potential. Carbon monoxide acts by reversibly binding to the heme group in hemoglobin, forming carboxyhemoglobin (COHb)[12]. As a result, less oxygen will be carried by blood to tissues during carbon monoxide inhalation. That means organs, such as the heart and the brain, having a critical need for oxygen would be the major target organs for carbon monoxide poisoning. Indeed, data indicate that carbon monoxide's toxicity is manifested primarily on its effects on the heart and the brain[4]. However, it should be pointed out that not all COHb levels are harmful to the health. For instance, the normal metabolism of heme generates carbon monoxide inside the body, leading to a COHb level of 0.4-0.7%, which does not result in adverse effects[4].

Due to the fact that carbon monoxide's toxicity is correlated with the COHb level in the blood, the SMACs were set according to safe COHb levels and the toxicity data were reported in terms of the COHb levels. The COHb level will rise with time as an individual inhales carbon monoxide and it would reach a plateau within 24 hours[13]. The resulting COHb level of a carbon monoxide can be calculated using the Coburn-Forster-Kane (CFK) equation[13].

4.2. Toxicity Information on Carbon Monoxide

The most important information for the establishment of SMACs is the information on the toxic effects of the chemical. To facilitate the setting of short-term and long-term SMACs, toxicity information on carbon monoxide was separated into three categories: acute, subchronic, and chronic.

4.2.1. Acute Toxicity

This subsection summarizes the toxicity of carbon monoxide in humans after an exposure ranging from several minutes to 8 hours. A COHb level of 70% is lethal, while 50-60% leads to coma and convulsions[4]. Headache, nausea, and vomiting are detected are detected at 15-40% COHb[14,15]. Increased frequencies of ventricular premature depolarization were seen in coronary patients at 6% COHb[16]. A COHb level of 5% is known to increase reaction time and impair hand-eye coordination[11,17]. Finally, carbon monoxide reduces the maximal exercise duration at 3.4% COHb[18].

4.2.2. Subchronic Toxicity

This subsection summarizes the toxicity produced by carbon monoxide exposures lasting longer than one day. A continuous exposure of humans to carbon monoxide for 7 or 8 days resulting in 2.4% COHb has been shown to produce heart rhythm changes[19]. New York employees working in a tunnel with, on the average, 38 ppm carbon monoxide, as well as other automobile exhaust pollutants, showed a higher mortality from arteriosclerotic heart disease[20]. However, whether subchronic carbon monoxide exposures cause arteriosclerotic heart diease is still not certain.

There are a lot of data on carbon monoxide's subchronic toxicity gathered in laboratory animals, but only the more important data will be described here. As discussed above, carbon monoxide intoxication primarily produces toxicity on the brain and the heart. However, animal studies demonstrated that, in subchronic exposures, carbon monoxide could also cause increases in hemoglobin concentration in the blood. For instance, a continuous, 6-month exposure of dogs to 50 ppm carbon monoxide, which is equivalent to 7.3% COHb, increased the hemoglobin concentration by 12%, but it did not cause any changes in the EKG[21]. Similarly, a continuous, 90-day exposure of rats to 96 ppm carbon monoxide (equivalent to 7.5% COHb) increased both the hemoglobin concentration and the hematocrit[22].

The increases in hemoglobin and red blood cells probably represent an adaptation of the body to the subchronic deficiency of oxygen supply to tissues. It should be noted, however, that there are species differences in this adaptive response. No increases were seen in monkeys exposed to 66 ppm of carbon monoxide, reaching a COHb level of 7.4%, for 2 years[23]. It took a much higher level of carbon monoxide exposure for such an adaptive response to occur in the monkey. A continuous exposure of monkeys to 200 ppm carbon monoxide (equivalent to 16 to 20% COHb) increased the hematocrit and hemoglobin level[22]. Because humans are biologically closer to monkeys than to the dog or rat and because astronauts are not expected to encounter high levels of carbon monoxide for a long time, this adaptive response of the body toward subchronic carbon monoxide most likely would not occur in the astronauts. As a result, the adaptive response was not considered in setting the carbon monoxide SMACs.

4.2.3. Chronic Toxicity

There are no data on the toxic effects of a carbon monoxide exposure lasting almost the normal life span of an adult.

4.3. Rationale Used to Set the Short-term SMACs

In an acute carbon monoxide exposure, the lowest COHb level that has been found to adversely affect the body is 3.4%, which reduced the maximal exercise duration by 5% in human volunteers[18]. Since a mere 5% reduction in the maximal exercise duration would not significantly impair the astronauts in an emergency, the exercise effect of 3.4% COHb is considered acceptable in short term. Therefore, the second lowest toxic COHb level is chosen to be the criterion for setting the 1-hour and 24-hour SMACs.

A short-term exposure to carbon monoxide, yielding a COHb level of 5%, is known to cause CNS impairment, such as an impairment of hand-eye coordination and an increase in reaction time[17]. The short-term SMACs should be set to prevent CNS impairment because CNS impairment would interfere with the astronauts' ability to deal with an emergency. The task is to estimate a COHb level that would not cause CNS impairment. Because 5% COHb appears to be the threshold for causing CNS impairment in humans[11] and because an 1-hour exposure to carbon monoxide at the 1-hour National Ambient Air Quality Standard would yield a COHb level of about 3% in exercising subjects[6], the 1-hour and 24-hour SMACs are set at a level that would produce no more than 3% COHb in the astronauts. Using the hemoglobin concentration determined inflight during the Skylab missions[24], the 1-hour and 24-hour carbon monoxide exposure concentrations that would yield a 3% COHb were calculated with the CFK equation[13]. The 1-hour and 24-hour exposure concentrations were calculated to be 55 ppm and 20 ppm, respectively. The 1-hour and 24-hour SMACs were set at 55 ppm and 20 ppm, respectively.

4.4. Rationale Used to Set the Long-term SMACs

In setting the 7-day SMAC, the toxicity data from an 8-day carbon monoxide exposure of human subjects were utilized[19]. In that study, an 8-day exposure to 15 ppm carbon monoxide resulted in 2.4% COHb and caused P wave changes in the EKG. Therefore, the 7-day SMAC should be established to prevent any EKG changes induceable by carbon monoxide. It has been calculated that an 8-hour exposure of exercising individuals to the EPA's 8-hour National Ambient Air Quality Standard would yield a COHb of 1.6%[6]. It is reasoned that if 1.6% COHb is safe for the general population, 1.6% COHb should also be safe for astronauts. The 7-day SMAC is the carbon monoxide exposure concentration that would yield 1.6% COHb in a 7-day exposure. That SMAC was calculated to be 10 ppm, applying the Skylab hemoglobin concentration in the CFK equation.

The use of the hemoglobin concentration determined during the Skylab missions in the 7-day SMAC calculation corrects for the microgravity-induced reduction in red cells. Even though cardiac arrhythmias were detected in the astronauts during the Skylab mission[25], no correction was made for the potential synergistic effects of carbon monoxide and microgravity on the heart. The reason is that the 7-day SMAC is based on the 8-hour National Ambient Air Quality Standard, which was designed to protect the general population and the astronauts are much healthier than the infirmed or the aged in the general population.

There are no human data on carbon monoxide's toxicity for an exposure lasting longer than 8 days. The subchronic data gathered in laboratory animals[21-23] were not relied upon in setting the 30-day and 180-day SMACs because the most sensitive endpoints, i.e., CNS impairment and cardiac arrhythmias, were not reliably determined in these studies. The target COHb level of the 7-day SMAC of 1.6% was chosen to be the target COHb level for the 30-day and 180-day SMACs. A COHb level of 1.6% should provide a sufficient safety margin for the astronauts in a 30- or 180-day carbon monoxide exposure. The reason is that 1.6% is not much higher than the COHb level of 0.7-1.0% measured in nonsmokers[26] and it is also lower than the COHb level of 3% or 4-5% in smokers[27,28]. With the CFK equation, the 30-day and 180-day SMACs were calculated to be both 10 ppm[13].

5. CONCLUSION

After reviewing information on the toxicity, absorption, metabolism, and pharmacokinetics of a chemical, the toxicologist must systematically sort the data and identify the toxic endpoints that a SMAC must protect against. By applying toxicological principles to the appropriate data on the toxic endpoints, the safe exposure concentration is then estimated for a given exposure duration and such a concentration is the SMAC for that exposure duration. This paper demonstrates the approach using carbon monoxide as an example.

6. REFERENCES

1. Office of Space Transportation Systems, "Flammability, Odor, and Offgassing Requirements and Test Procedures for Materials in Environments that Support Combustion", NHB 8060.1B, NASA, Washington, DC, September 1981.

2. NRC's Committee on Toxicology, "Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants", Vol. 4., National Academy Press, Washington, D.C., 1985, p. 17.

3. Coburn, R.F., et al., "Considerations of the physiology and variables that determine the blood carboxyhemoglobin concentration in man", J. Clin. Invest., Vol. 44, 1964, pp. 1899-1910.

4. Stewart, R.D., "The effect of carbon monoxide on humans", Ann. Rev. Pharmacol, Vol. 15, 1975, pp. 409-423.

5. Lawther, P.J., "Carbon monoxide", Br. Med. Bull., Vol. 31, 1975, pp. 256-260.

6. Rylander, R. & Vesterlund, J., "Carbon monoxide criteria", Scand. J. Work Environ. Health, Vol. 7, Suppl. 1, 1981, pp. 1-39.

7. Huntoon, C.L., et al., "Hematology, immunology, endocrinology, and biochemistry", SPACE PHYSIOLOGY AND MEDICINE, Ed. Nicogossian, A.E., Lea & Febiger, Philadelphia, PA, 1989, pp. 222-239.

8. Bungo, M., "The cardiopulmonary system", SPACE PHYSIOLOGY AND MEDICINE, Ed. Nicogossian, A.E., Lea & Febiger, Philadelphia, PA, 1989, pp. 179-201.

9. Crump, K.S. & Howe, R.B., "The multistage model with a time-dependent dose pattern: Applications to carcinogenic risk assessment", Risk Anal., Vol. 4, 1984, pp. 163-176.

10. Jones, H.A., et al., "Rate of uptake of carbon monoxide at different inspired concentrations in humans", J. Appl. Physiol., Vol. 52, 1982, pp. 109-113.

11. Ramsey, J.M., "Carbon monoxide, tissue hypoxia, and sensory psychomotor response in hypoxaemic subjects", Clin. Sci., Vol. 42, 1972, pp. 619-625.

12. Laties, V.G. & Merigan, W.J., "Behavioral effects of carbon monoxide on animals and man", Ann. Rev. Pharmacol., Vol. 19, 1979, 357-392.

13. Peterson, J.E. & Stewart, R.D., "Predicting the carboxyhemoglobin levels resulting from carbon monoxide exposures", J. Appl. Physiol., Vol. 39, 1975, pp. 633-638.

14. DiMarco, A., "Carbon monoxide poisoning presenting as polycythemia", N. Engl. J. Med., Vol. 318, 1988, p. 874.

15. Stewart, R.D., et al., "Experimental human exposure to carbon monoxide", Arch. Environ. Health, Vol. 21, 1970, pp. 154-164.

16. Sheps, D.S., et al., "Production of arrhythmias by elevated carboxyhemoglobin in patients with coronary artery disease", Ann. Intern. Med., Vol. 113, 1990, pp. 343-351.

17. Putz, V.R., et al., "A comparative study of the effects of carbon monoxide and methylene chloride on human performance", J. Environ. Pathol. Toxicol., Vol. 2, 1979, pp. 97-112.

18. Horvath, S.M., et al., "Maximal aerobic capacity at different levels of carboxyhemoglobin", J. Appl. Physiol., Vol. 38, 1975, pp. 300-303.

19. Davies, D.M. & Smith, D.J., "Electrocardiographic changes in healthy men during continuous low-level carbon monoxide exposure", Environ. Res., Vol. 21, 1980, pp. 197-206.

20. Stern, F.B., et al., "Heart disease mortality among bridge and tunnel officers exposed to carbon monoxide", Am. J. Epidemiol., Vol. 128, pp. 1276-88.

21. Musselman, N.P., et al., "Continuous exposure of laboratory animals to low concentration of carbon monoxide", Aerosp. Med., Vol. 30. 1959, pp. 524-529.

22. Jones, R.A., et al., "Effects on experimental animals of long-term inhalation exposure to carbon monoxide", Toxicol. Appl. Pharmacol., Vol. 19, 1971, pp. 46-53.

23. Eckardt, R.E., et al., "The biologic effect from long-term exposure of primates to carbon monoxide", Arch. Environ. Health, Vol. 25, 1972, pp. , 381-387.

24. Kimzey, S.L., "Hematology and immunology studies", BIOMEDICAL RESULTS FROM SKYLAB, Ed. R.S. Johnson & L.F. Dietlein, 1977, NASA, Washington, D.C., p. 249.

25. Smith, R.F., et al. (1977). "Vectorcardiographic changes during extended space flight (M093). Observations at rest and during exercise", BIOMEDICAL RESULTS FROM SKYLAB, Ed. R.S. Johnson and L.F. Dietlein, 1977, NASA, Washington, D.C., pp. 339-350.

26. Radford, E., et al., "Blood carbon monoxide levels in persons 3-74 years of age in the United States, 1976-80", Advance Data Report No. 76, 1981, National Center for Health Statistics, Hyattsville, MD.

27. O'Hanlon, J.F., "Preliminary studies of the effects of carbon monoxide on vigilance in man", BEHAVIORAL TOXICOLOGY, Ed. B. Weiss & G. Laties, 1975, Plenum Press, N.Y., pp. 61-75.

28. Horvath, S.M., et al., "Maximal aerobic capacity at different levels of carboxyhemoglobin", J. Appl. Physiol., 1975, pp. 300-303.

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