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Chapter 2

TOXICOLOGY OF THE AIR IN CLOSED SPACES

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Spacecraft engineering and design for life-support services is restricted to meeting the minimum biologic needs of the astronauts. These restrictions arise from the mass, volume, energy, and associated cost requirements for providing more than minimal life-support services.

This chapter is concerned broadly with providing man's minimal physiologic requirements without significant impairment of health or functionality. The more specific concern is to identify those factors of spacecraft construction and operation that may interfere with meeting man's minimal atmospheric needs. The qualitative and, wherever possible, quantitative description of the quality of the atmosphere in the spacecraft are discussed. In particular, this chapter is devoted to a consideration of those atmospheric contaminants which may have an adverse effect on the health and functionality of astronauts.

The sources and compositions of these contaminants in the atmosphere of the craft will be identified. Their potential effects on the human body will be considered individually and collectively insofar as the data permit. The establishment of acceptable concentrations for toxic agents in the artificial gaseous atmosphere (hereafter referred to as AGA) of the spacecraft is a matter of balanced judgment of their risks, benefits, and costs. Finally, this chapter will summarize experience so far with the establishment of acceptable concentrations, and call attention to areas of uncertainty needing further investigation.

In 1966, V. V. Parin [77] pointed out that in spite of large-scale achievements and the great volume of experimental data collected, space biology and medicine were only at the initial stages of development. The increased tempo of space flights has placed greater demands on space biology and medicine, resulting in intensified study of man's reactions to space flight. The results of some of these studies will also be discussed.

The isolation of people and equipment in hermetically sealed environments can result in gradual accumulation of airborne contaminant chemicals and microflora up to toxic or infectious magnitude. Experience with such environments is not totally lacking. The situation in submarines and other underwater habitats resembles in many ways the conditions in spacecraft. There are at least three important differences: (a) the amount of space and energy available per person is much less in the spacecraft, (b) the ability to return rapidly to a normal environment is greater in a submarine, and (c) the completely unknown effect of weightlessness is a factor in space flight.

[1] With contributions from V. P. Savina and S. N. Zaloguev, USSR, and E. M. Roth, USA.

SOURCES AND IDENTIFICATION OF CONTAMINANTS IN THE ARTIFICIAL GASEOUS ATMOSPHERE (AGA)

The spacecraft AGA is a dynamic mixture of the gas or gases which might be deliberately provided for respiration such as oxygen, nitrogen. water, and carbon dioxide. There are other components considered contaminants which are undesirable, if not potentially dangerous, and which must be controlled. Even those essential gases added deliberately must be controlled within limits to avoid adverse effects. The contaminants have several origins including biologic (man and microorganisms), materials (construction and supplies), processes (electrical, life support), and external (electromagnetic and heavy particle radiation); they may be produced during normal operations or emergencies (leaks). These contaminants have been reviewed by Ross [84]. The nature, and especially the amount of AGA contaminants from these sources, will vary with the duration of the space flight.[2]

The concentration of contaminants at equilibrium and the time to reach this concentration are determined by the variables of Equations (1) and (2) [86]. These are key factors in establishing the rate of removal needed to attain a given equilibrium level in the atmosphere.

$$C=\frac{W}{b}\left(1-e^{\frac{-bt}{a}}\right) \qquad (1)$$

where,

C = mg/m³ of contaminant at time t;
W = mg contaminant generated/day;
b = m³ atmosphere leaked/day at x psia;
t = days elapsed time;
e = 2.718

This equation suggests that an equilibrium level of contaminant will be reached. The time to reach 99% of equilibrium concentration after closure can be estimated by the equation:

$$t_{\text{days}} = 4.6a/b \qquad (2)$$

where,

a = m³ total effective volume
b = m³ leak/day at x psia

In evaluating the buildup rate, important secondary factors to be considered for each contaminant are the kinetics of sorption along adsorption beds and the breakthrough curves for such gas bed systems. These curves also determine the nature and timing of secondary chemical reactions which can occur on the bed and thus the alteration in the nature of the trace contaminants to be considered.

Biologic Sources – Microflora

The growth of microorganisms can be expected in spacecraft on surfaces in addition to those of the human body. Bacteria, fungi, and possibly algae will grow on surfaces of the spacecraft if there is sufficient adsorbed nutrient and water. Experiments have been described with men in chambers simulating certain factors of space flight under different regimes of work and rest. Along with physiological, psychological, and clinical investigations, attention was given to the microflora of the chamber and skin of the occupants, and the immunologic reactiveness of the men. Significant changes and interactions were found in the microbial system [12].

Popov and coworkers utilized small, closed rooms which had been disinfected, had practically no influx of dust, with controls for composition, temperature, and circulation of air. They found that contamination of skin and clothing of the occupants was only minimally affected by dust from clothing, footwear, furniture, and other equipment. Possible sources of contamination were: food residues, untrapped urine and feces, and bacterial aerosols. The important and continuously active source of skin contamination to the occupant's skin was the skin itself [12].

Table 1 illustrates the increase of microbial content in the air and the effect of an air purification system in a sealed chamber occupied for 120 days. The level of microbial contamination of air depends on the duration of man's stay, number of crewmembers, conditions of their work, filtering capability and cycling of the

[2] The numerous valuable contributions of Kustov and Tiunov are worthy of note and several are cited in this chapter [43, 44, 46, 100, 101].

mechanical system of purification from chemical substances, and regeneration of air. It also depends on the presence of special disinfectant apparatus, and gas composition of the atmosphere. Along with the increase of general bacterial contamination of the air, there are shifts in the yeasts and other specific microflora present with an increase in the proportion of pathogens. For example, a small but significant increase in the population of *Candida* sp has been noted as well as saprophytic white staphylococci, diphtheroids, bacilli, and sarcinae. The skin microflora vary among individuals, which is to be expected, but these differences soon disappear upon confinement in real or simulated spacecraft [59, 70, 73, 113].

Since animals have been flown in spacecraft, it is important to consider their microflora also. Sitnikova's observations on animals in experimental chambers revealed that the quantity of microorganisms in the air increased fivefold, and there was a shift to predominance by types of organisms more resistant to the effects of the air such as spores, aerobes, and molds. It has also been suggested that animals in sealed chambers might develop a reduced resistance to virus infections [12, 70].

The effect of the air composition on the microbial population, as noted above, has also led to the suggestion by Borsenko et al [70] that the AGA might be adjusted to produce a decrease in bacterial contamination of the air. However, this subject has not received much study. Similarly, little attention has been given to contamination of the AGA by gases released by the microflora. Korotaev and coworkers [43] have established that the algae, *Chlorella*, release toxic materials including carbon monoxide. The CO formation is related to oxidation of the tetrapyrrole nucleus in the chlorophyll molecule.

TABLE 1.—*Average Microfloral Contents of Air, Skin, and Pharynx of Subjects Tested at Different Periods of a 120-Day Experiment* (After [70])

Index (total count)	Before experiment	Experiment period, days								Days after experiment		
		1–15	16–30	31–45	45–60	61–75	76–90	91–105	106–120	1–15	16–30	31–60
In 1 m³ air	1500	7500	12 000	14 000	7500	17 000	14 000	30 000	3000[1]			
On 1 cm² skin	30	56	66	66	60	53	53	66	30[1]	39	30	31
In 1 cm³ pharynx washings	34	66	74	37	10	102	58	168	33[1]	30	28	30

[1] On days 106–120 of the experiment, the low level of microbial infestation is related to the development and use of a system in the hermetic chamber for purifying air from microorganisms.

According to the Soviet experience, the following rules seem to characterize the microbial content of the AGA:

1. There are periodic increases in the number of microflora.
2. Each quantitative increase is accompanied by a change in the qualitative composition.
3. The skin microflora indicate development of the phenomenon of dysbacteriosis.
4. Each periodic increase includes an increase in the proportion of skin microflora having pathogenic properties or increased resistance to antibiotics of the penicillin and tetracycline groups [12, 49, 70].

Biologic Sources—Man

All the excretory products of man contribute to the gaseous pollution of the AGA in the spacecraft, which are released into the spacecraft from lungs, gastrointestinal tract, urinary tract, skin, hair, and mouth [12, 86].

Respiratory. The lungs release water, carbon dioxide, and carbon monoxide predominantly. The rate of carbon monoxide exhalation from normal degradation of hemoglobin by one person is about 0.4 ml/h. Analysis of the exhaled air of healthy young adults showed these minor contaminants present: ammonia, formaldehyde, acetaldehyde, acetone, methylethyl ketone, methanol, propanol, butanol, formic acid, acetic acid, propionic acid, methane, ethane, and higher hydrocarbons [71, 94, 100, 109].

Gastrointestinal. The gastrointestinal excretions are feces, flatus, and urine. Their gaseous components include indole, skatole, carbon dioxide, hydrogen, hydrogen sulfide, methane and other hydrocarbons, nitrogen and its oxides, aliphatic acids, phenols, oxygen, and various mercaptans. The latter depend to a great extent on the diet. Nearly 150 specific compounds have been identified in urine, very few of which are volatile until degraded by bacteria, whereupon the principal air contaminant is ammonia. Details of the amount and composition of feces, flatus, and urine have been tabulated by Roth, Wheaton, and Grace [12, 109].

Integument. The skin and its sweat glands are the sources of volatiles such as ammonia and phenols along with numerous trace materials. The skin and the hair are also sources of particulate matter that will be suspended in the air. These desquamated scales consist of proteins and lipids and carry numerous microorganisms. Their particle size is too large to be of any health significance but they may create mechanical problems in the spacecraft's equipment [109].

In view of the contaminants described, it is clear that man in a sealed environment becomes an important source of toxic contaminants. These impurities in the AGA must not be permitted to accumulate above safe levels.

Materials

Materials currently being used in US manned spacecraft were listed at the NASA Manned Spacecraft Center in Houston, Texas [33]. Kustov and Tiunov have reviewed the experience with USSR spacecraft materials [46].

Compounds of relatively high vapor pressure are outgassed from solid materials and from the hydrocarbon lubricants and operating fluids of machines. They originate from such sources as plastics, toilet articles, lubricating compounds, insulations, paints, adhesives, and residual solvents from degreasing treatments.

The rate and composition of outgassing for various spacecraft materials have been studied [19, 74, 81]. The oxygen content and temperature of the atmosphere alter the rate and composition for the products. Intermittent purging of the atmosphere is also a variable to be considered in predicting contaminant outgassing and accumulation rates. Compounds continue to be outgassed after 90 days' exposure to space cabin atmospheres. The outgassing characteristics and other design parameters for nonmetallic components of US spacecraft have recently been incorporated in a handbook available from the Manned Spacecraft Center [73].

A special panel, convened in 1967 under the Space Science Board of the US National Academy of Sciences, was concerned with outgassing products in confined spaces. Their report tabulates more than 300 compounds detected in various US spacecraft and flight simulations [66].

Processes

The numerous processes carried out aboard a spacecraft are another significant source of AGA contaminants, many of which are in the form of solid or liquid aerosols.

Cooking may release such gases as acrolein, carbon monoxide, and formaldehyde along with solid particulates as smoke. Personal hygiene procedures, including washing and shaving, produce aerosols. Ozone may be produced by electrostatic precipitators used to remove particles from the air. It may also be produced by ultraviolet radiation used for controlling microorganisms. Any electrical apparatus having a corona or spark discharge will also form ozone.

Many of the proposed systems for recovering oxygen from carbon dioxide during long flights operate at elevated temperatures. If the AGA contains halogenated organic compounds they may be partially or totally decomposed when passing through the oxygen regenerators. The decomposition products are often more toxic than the original impurity. Alkaline processes for removing carbon dioxide can generate sufficient heat to create similar problems.

One reaction of this type is of special concern in the spacecraft. Its starting materials are the halogenated solvents used for degreasing equipment prior to assembly or for solvents in paints and other coatings. Traces of these often remain to be outgassed later during space flight and may then be decomposed as:

$$Cl_2C{=}CHCl \xrightarrow[\text{alkali}]{\text{heat and/or}} ClC{\equiv}CCl + HCl$$

The trichloroethylene is considered moderately toxic, the HCl is an irritant, but the dichloroacetylene is extremely toxic. This problem has been reviewed in detail [66].

Spacecraft contain numerous heat transfer systems which involve fluids having detectable vapor pressures. Small leaks of these fluids can produce a gaseous contaminant as well as an aerosol.

Aerosols

In view of the numerous sources (bacteria, man, materials) and aerosols (solid or liquid), it is of value to consider some of the properties of aerosols in relation to their behavior in the weightlessness condition of space flight.

Even *nontoxic* particulates may be a hazard in space operations because of the zero-gravity environment [9]. In reviewing toxic hazards, there must be concern that aerosols can act as adsorbents or condensing nuclei for toxic gases [90]. This facilitates entrance into the lower respiratory tract of materials which, because of their high water solubility, are generally trapped in the upper respiratory tract. It also provides for local areas of extreme irritation due to concentration of the toxic gas at the locus of impaction.

The problem, which is unique in the closed living space, is the tendency of aerosol particles to increase with time in numbers and mean diameters.

Theoretical considerations of the role of zero gravity in the properties of aerosols imply that the amount of particle or droplet contamination inhaled in orbit could be increased over the amount inhaled in a similar situation under 1-*g* environment [10]. The following data and conclusions are taken directly from the Busby and Mercer study [10].

> The predicted characteristics of particle and droplet deposition in the respiratory passages for the weightless environment show that in space, as on Earth, the nose or mouth should continue to operate as highly efficient filters, protecting the lower respiratory passages from all particles and droplets above about 10 μm diam. Fortunately, this size is considerably less than that of particles and droplets of most contaminants which might be introduced into the spacecraft cabin atmosphere. Theoretical *deposition curves* predict that fewer inhaled particles and droplets, having diameters between about 0.5 and 10 μm, will be deposited in lower respiratory passages in a weightless environment, than in one of unit gravity. Substitution of helium or another gas for nitrogen would, in this pressure range, alter viscosity by only a few percent, hence should not alter these deposition curves significantly. There are no definitive empirical data to support these theoretical curves.

Under conditions of Earth gravity, retention of particles in diameter size 0.2 to 5 μm varies between 20 and 90%. Of the particles gaining entrance to the lower respiratory tree, maximum retention is for 1-μm particles and minimum retention is at 0.4 μm. The disposition of these deposited particles depends on their solubility. Those which are water-soluble are rapidly absorbed into the blood stream and a toxicologic effect may occur in a short time. Less soluble substances and those deposited on the upper airways are moved by the flow of mucus and by ciliary action to the pharynx, where they enter the gastrointestinal tract. An excellent review of the deposition, clearance, and retention of inhaled particulates was prepared by Middleton and his committee, concerned with an air pollution standard [54].

Ionized aerosols have been discussed often as a cause of behavioral changes during various meteorological phenomena [45]. Other biologic effects, such as those on tracheal cilia and on lower biologic forms, have also been reported. The concentration of aerosol ions in the natural or submarine atmospheres has always been small, averaging about 450 (+) ions and 250 (−) ions/cm³ [42]. No data have been obtained in operating space cabins. In view of the low concentration of aerosol ions in submarines and the uncertain significance of the experiments with isolated tracheal preparations, the potential significance of these aerosols in space cabins is not clear. The problem has been discussed by Nefedov [69].

Malfunctions and Emergencies

In addition to materials present during normal operations, the toxic atmospheres resulting from fire or equipment failure must be considered. Accidents in the launch and preparation areas, as well as on board future spacecraft where extravehicular maneuvering units may be serviced, can lead to exposure to vapors and aerosols of rocket fuels and oxidizers from spills or leaks. Such exposures may lead to acute toxicity from relatively large doses of the compounds. Their toxic effects have been recently summarized [39].

Equipment malfunctions, especially those of electrical equipment, may cause overheating and thermal degradation of insulation. Fire in a spacecraft will produce combustion products along with decomposition products of any fire extinguishing materials used. In these situations, a variety of compounds of different degrees of toxicity will be formed, depending on the materials involved and the conditions of decomposition.

When high molecular weight materials are decomposed by heat, two general mechanisms are involved: depolymerization and fragmentation; both probably occur in all instances but in varying proportions. Monomer production is high from polytetrafluoroethylene, polymethylmethacrylate, and polymethylstyrene. The monomers and chain fragments may also react at high temperatures to form new materials, such as methanol, carbon monoxide, halogen acids, aldehydes, hydrogen cyanide, octafluoroisobutylene, and carbonyl fluoride. If metals are involved in overheating, for example selenium rectifiers, fumes of the metal and its oxides will be formed. Each material and each potential malfunction must be considered carefully in selecting items for spacecraft construction [1, 36, 90, 109].

The proposed transfer of spacecraft occupants from one ship to another poses special problems. What will be the effect on new personnel entering a ship whose environment is already contaminated with the gaseous, particulate, and microbial effluvia of a preceding crew? Will a period of double occupancy be required while the new crew becomes adapted sufficiently to assume control of the ship? Will a crew moving from a contaminated ship to a clean one or back to Earth experience any difficulties [72]?

Analysis and Monitoring

Qualitative and quantitative analyses of the vital gases and contaminants in the AGA are essential to protect the health of the astronaut. The variety of compounds and low concentrations of many challenge the sensitivity and accuracy of existing analytical equipment, especially those compatible with spacecraft. Consequently, the data obtained from space flights are limited and subject to inaccuracies.

The reproducibility of levels of toxic materials found in space cabin simulators has been recorded [14]. Detailed analyses of these materials illustrate the variability of data from sample to sample and laboratory to laboratory. At the present state of the art of analysis and sampling, any data on "the highest concentration" found in sealed cabins must be viewed with the appropriate level of skepticism suggested by these data.

Procedures are continually being improved and gas chromatographic techniques are commonly used. Current studies of infrared spectroscopy interferometry, double resonance microwave spectroscopy, mass spectrometry, and other new techniques, offer some promise for ground-based and possibly in-flight sampling and analysis [8, 14, 57, 83, 92, 99, 102]. The techniques and procedures used by the USSR have been described by Nefedov et al, who have also pointed out the need to monitor the AGA for microbial contamination [70, 71].

External Contaminants

Spacecraft and their occupants are subject to electromagnetic and heavy particle radiation, especially on exposure to a solar flare. These effects have recently been discussed by Grahn [67], and Lebedinskii [48].

Experience from both manned and unmanned Moon landings so far indicates that contamination of the craft by extraterrestrial materials will not present any new or magnified health hazards. This observation does not necessarily apply to human landings on other targets.

Odors

The human olfactory sense permits detection of vapors of many organic substances at concentrations of 10^{11} to 10^{13} mol/cm^3 air, and some at concentrations as low as 2×10^9 mol/cm^3 [17, 21]. There are also indications that substances at one-tenth the threshold may influence the odor quality of other odorants present at concentrations well above the threshold [40]. The use of the olfactory sense in detecting and diagnosing malfunctions in equipment systems has been thoroughly reviewed [31].

Fortunately, the human olfactory sense adapts to odors quite rapidly. Experiences in space cabins and space cabin simulators suggest that crews are not bothered by odors in the cabin which may overwhelm additional crew who are unacclimatized.

POTENTIAL BIOLOGIC EFFECTS OF SPACECRAFT AIR CONTAMINANTS

All compounds have an adverse effect on the body at some quantity or concentration. Upon absorption into the body, toxic substances may be processed in one or more of several ways. They may be retained or excreted unchanged; or biotransformed by oxidation, reduction, hydrolysis or conjugation to products less or more toxic. Through these processes, the body has the ability to accept a finite amount of any substance without injury, according to present knowledge. When the capacity of these processes is exceeded, there is an adverse effect, the magnitude of which is related to the amount of excess material absorbed. The relationship between causative dosage and resultant effect is not necessarily a constant proportionality over the entire range. This lack of proportionality in dosage-effect relationships makes extrapolations beyond the range of available data unreliable [61].

In most instances the body can repair the damage with no residual effect, although sometimes there is a permanent change, such as a scar. In such cases, the total permanent change from single or repeated exposure may be sufficient to cause detriment to the body. In a few, relatively rare circumstances, the initial injury can alter the body's physiological processes in specific tissues so that they function abnormally long after the causative agent has disappeared, examples of which are changes in hormone excretion or cellular proliferation to produce tumors [111].

The study of these effects, which constitutes the science of toxicology, is complicated by many variables such as differences due to sex, age, and species. These factors and others have been reviewed and discussed extensively [35, 86].

The present state of toxicological knowledge is not adequate for reliable prediction of the effects of most substances on an individual at any given dose. This is especially true for the space program for two reasons: the increased use of multi-ton quantities of high-energy physiologically reactive compounds with inherent increased possibility of accidental exposure; and the contemplated long-term space mission within a closed system, in which, unlike submarine conditions, unlimited power is not available for complete control of the atmosphere. For adequate toxicological information in both situations, the greatest need is for inhalation data. This has led to construction of numerous experimental laboratories with sealed chambers for studying the effects of toxic substances on man and animals. One of these has been described in detail [37].

Exposure or dose may be expressed in several ways. One describes the quantity in terms of

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weight or volume of material per unit weight of the animal, for example, mg/kg. When referring to the concentrations of a gas or particulate in the air, the terms parts per million (ppm), which is a volume-volume ratio, or mg/m^3 are generally employed. In air exposures, the time of contact in minutes or hours is included. In the space cabin environment with an altered partial pressure of the atmosphere, it has been suggested that $\mu mol/m^3$ or $mmol/25m^3$ may be a more reasonable way to express the data [66]. The latter unit gives a numerical value which, at 1 atm pressure and at 25°C, is the equivalent of ppm by volume (the units used for submarine standards and occupational exposures to gases and vapors). At the same time it expresses the molar concentration per unit of space volume and is, therefore, equivalent to partial pressure of the contaminant. Unfortunately, the toxicological literature does not yet make use of these latter expressions as standard terms.

The dose-response data from toxicity studies result in a sigmoid graph with the actual data being more or less scattered about a smooth curve because of variability between test animals. The least variability is at the dose producing 50% response. Abbreviations used are: lethal dose (LD) and lethal concentration (LC); the percent of animals affected is expressed by subscript 0, 50, 100, and so forth. When subscripts are not used, the value has probably been based on limited observations and lacks statistical validity. When time is a factor, such as for inhalation exposure, it must be given. For example, $LC_{50}/4$ h means the concentration most likely to be lethal to 50% of the animals upon exposure for 4 h.

Quantitative relationships of dose and response are exceedingly important in the theoretical and practical evaluations of toxic action. In general, the greater the dose, the more severe the response or more rapid its onset. With some substances, time is an equally important factor in determining effect. Mathematical modeling of these relationships has been discussed by Roth [86].

Acute Toxicity

The term acute toxicity refers to the adverse effects from single or multiple doses delivered in a short time, such as by inhalation for a few hours. These are relatively high doses. Data on the acute toxicity of spacecraft contaminants are needed for several purposes. They serve as a quick and inexpensive screening procedure for estimating degree of toxicity and nature of the toxic effect. Such data provide a useful guide to selection of materials for use in space. Acute toxicity data are vital to planning for long-term toxicity studies and are directly useful when planning for emergency situations.

The concepts and methods of acute toxicity determinations, reviewed by a US National Academy of Sciences committee under the chairmanship of Lehman [60], describe in some depth the various factors that can affect the outcome of acute toxicity testing.

A brief review. The significant acute toxic effects of AGA contaminants will be reviewed, but space will not permit detailed discussion of their action, such as effective concentrations. Their action may be noted over the entire range of a few parts per million to several percent by volume. The alcohols produce narcosis and are irritants to the eyes and respiratory tract at high concentrations. Methanol is unique for its specific injury to the optic nerves. The esters of acetic acid have properties similar to those of the corresponding alcohols. They are metabolized to the alcohol. The ketones also are irritants and depressants of the central nervous system, and their odors can cause nausea at high concentrations. The aldehydes are strong irritants, generally stronger than the related ketones or alcohols and esters.

The acute toxicity of acetone for man in a sealed chamber has been reported by Mikhailov [56]. Concentrations of 0.44 and 0.55 mg/m^3 produced changes, respectively, in the electrocortical reflex and in the light sensitivity of the eye. Physiological compensatory changes for these effects were noted and it was concluded that short-term exposures up to 10 mg/m^3 are safe for man. Similar effects might be expected from many other oxygenated compounds at different concentrations.

The saturated alicyclic and aliphatic hydrocarbons are relatively mild in toxic action. High concentrations lead to narcosis. There is a possibility that very high concentrations may also affect the cardiovascular system. The toxic action of acute exposure to aromatic hydrocarbons is primarily depression of the central nervous system. Many compounds of this class are irritating.

Halogenated aliphatic compounds vary widely in the nature and severity of their acute toxicity; most cause narcosis and many injure the kidneys. Several are especially powerful agents for producing cardiac arrhythmias.

The heterocyclic compounds have few physiologic actions in common; the majority have distinct odors but toxic effects are diverse.

The inorganic gases encountered in spacecraft are respiratory irritants with the exception of carbon oxides. The action of most inorganic gases is exerted in the upper part of the respiratory tract, but a few, such as phosgene, penetrate deeply into the lungs. The carbon oxides, CO and CO_2, produce significant effects in acute exposures and deserve more detailed discussion.

Carbon dioxide is a normal component of air and a constituent of expired air resulting from metabolism. At concentrations above the normal physiologic range it stimulates the respiratory center and causes increased respiration. Concentrations of 7 to 10% by volume may produce unconsciousness, even if oxygen content is maintained at normal levels.

When carbon monoxide is inhaled, it reacts with hemoglobin to form the relatively stable compound, carboxyhemoglobin (COHb). This reaction utilizes the same bonding sites in hemoglobin as those for transporting oxygen from lungs to tissues. The result is anoxia at the cellular level throughout the body. It is more convenient and reliable to relate atmospheric CO to the percent of hemoglobin converted to COHb, which in turn can be related to toxic action. The heart and central nervous system are most sensitive to this effect. The cardiac effects are, of course, more critical during periods of heavy exercise or heat stress and may be significant at levels as low as 5% COHb. It has been suggested that subtle central nervous system effects result from COHb concentrations around 10%. A recent review of the toxicity of CO [68] includes a computer program developed by Roslinski for the equation introduced by Coburn [13], which relates CO exposure to bodily uptake. This equation correlates closely with experimental data.

The Coburn equation includes the CO produced endogenously by metabolism of hemoglobin, but does not directly allow for increased endogenous CO resulting from radiation-induced hemolysis. It has been shown that a dose of 600 R will produce an increase of $10.7\% \pm 1.3$ in the blood carboxyhemoglobin with concomitant decrease in the oxygen transport capacity [69].

The actions of microflora on spacecraft crews, a form of acute toxicity, should be considered. The normal bacterial flora in man's skin, mucous membranes, and intestines have been thoroughly reviewed [82] with special emphasis on differences in flora of various body sites. The microbiological changes in sealed chambers have already been discussed. The tendency toward increased total skin flora, especially in axillary, groin, and other fold areas [20, 23, 26, 82], is augmented by wearing a space suit and by high humidity [22]. The increasing bacterial population tends to reach a plateau after variable periods in a given environmental situation [12]. There is an exchange of fecal and skin flora among enclosed subjects with no tendency for pathogens to become predominant [32, 72]. Throat flora are exchanged less rapidly [23]. Little is known about the viral population in sealed systems. Subtle interactions between the gaseous environment and host may alter viral infectivity [28].

Chamber studies so far indicate no tendency toward decreased body resistance to pathogens [50]. Pathogens have been transferred from subject to subject with no outbreak of infection [23]. Presence of 100% oxygen at 5 psia does not appear to alter greatly animals' susceptibility to pathogenic infections [58]. It would be expected that the isolated spacecraft environment would eliminate exogenous infectious disease. However, radiation and subacute stress may alter response to enable normal flora to become pathogenic in future missions, but no problems have arisen so far. In nuclear submarines with large crews, there tends to be a flurry of infectious disease of primarily respiratory type in the first few weeks of a cruise, but this incidence drops rapidly as *herd immunity* develops [110]. This pattern may be expected in future large space crews. The problem of microbial shock in space missions of long duration is still a hypothetical one [51].

New personnel, introduced into spacecraft that have been occupied for some time, may require a period of adaptation. Another consideration that affects crew safety is the effects of microbial flora on equipment. Filter beds clogged after prolonged exposure may be another, more subtle engineering problem, and fungi can cause the deterioration of electronic components [86].

Chronic Toxicity

Chronic toxicity usually refers to adverse effects of chemicals on the organism from repeated or continuous exposures lasting months or years. The quantities involved at any one time are relatively small. Occasionally it also refers to delayed effects from which recovery is slow. Unless otherwise indicated, this discussion applies to the first meaning.

The concepts and methods of chronic toxicity determinations were reviewed by the US Food and Drug Administration in 1959 [5]. The methods described are essentially those used today. An extensive, diverse literature on more recent methods will probably be consolidated by one or more authors in the near future. Animal responses to continuous exposure as measures of human response may not be entirely correct in all instances [34].

First consideration for chronic toxicity must be the AGA itself, especially its vital component oxygen. Our knowledge of oxygen toxicity indicates that excursions of only a few percent above the normal partial pressure can cause serious effects to the central nervous system as well as other vital tissues. These physiologic principles were reviewed by Roth in the *Bioastronautics Handbook* [109]. Golberg has provided a more recent, although brief, review [30]. Marked cardiovascular effects were described by Wood in 1972 [112].

Comments on the chronic toxicity effects of specific compounds in the AGA (which follow) are intended to identify possible critical problems but in no way are complete discussions of the materials' toxicity.

Alcohol concentrations which might be encountered continually in spacecraft AGA are probably low enough to be fully metabolized to CO_2 and H_2O with no adverse effects. Precautions are necessary to avoid accumulation of alcohols that will produce absorbed levels greater than the metabolic capacity of the body. This level is limited for methanol by the excretion rate of formic acid, the end product of methanol metabolism. Excess formic acid upsets the body's acid-base balance. It has been postulated that blindness caused by high doses of methanol is due to specific action of formic acid on the optic nerves [111]. Liver enlargement is also found in such circumstances.

Higher molecular weight alcohols, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl, upon chronic exposure, lead to liver and kidney damage usually at concentrations well below those producing narcosis and below those found irritating [8].

Esters of these alcohols with acetic acid are found. The first noticeable effect of chronic exposures with increasing concentrations is hypotension and irritation followed at higher concentrations by pulmonary edema, liver and kidney damage, and narcosis [78].

The chronic toxicity of ketones seems related to their irritancy with little or no cumulative toxic effects since they are readily metabolized at low concentrations [111]. The same may be said of the aldehydes; however, their control level must be lower than that of the corresponding ketones to avoid pulmonary edema [78].

The aliphatic and aromatic hydrocarbons, with the exception of benzene, are only slightly toxic at low concentrations of chronic exposures. Mild irritation of vital organs and narcosis are found at higher levels. Benzene is well-known for its ability to damage the bone marrow leading to anemia and leukemia. Benzene should be rigidly controlled because of the seriousness and irreversibility of its effects [27].

The chlorinated hydrocarbons, $CHCl_3$, $ClCH_2{-}CH_2Cl$, $Cl_2C{=}CCl_2$, CH_3CCl_3, have all been detected in the AGA of spacecraft. Chronic exposures can lead to liver and kidney injury, which does not appear to happen with the chlorofluoro-hydrocarbons $ClCF_3$, Cl_2CF_2, $FCCl_3$, and Cl_3CCF_3 which have also been found in spacecraft. The latter compounds have very low chronic toxicities. All halogenated hydrocarbons should be considered as capable of causing cardiac arrhythmias and each should be studied carefully for this factor. These compounds have another feature in common: thermal decomposition to toxic products, a degradation enhanced by alkaline conditions. The products include the halogenated acids, HCl, and HF, which are irritants, and most importantly may also include the highly toxic chlorinated acetylenes. The latter attack the nervous system, especially the trigeminal nerve causing paralysis [89].

Among the heterocyclic compounds, a variety of chronic toxic effects is found. Skatole can be a depressant of the circulatory and central nervous systems [87]. Furan will produce reversible liver changes [96]. Liver and kidney injury has been found from both dioxane and indole but more importantly, both compounds have been reported to produce cancer in animals [4, 18].

Of the inorganic gases and vapors found in the AGA of spacecraft, ammonia is perhaps the most innocuous. Its ready solubility in the moisture layer of the upper respiratory tract and prompt metabolism lead to the conclusion that it is unlikely to cause any systemic toxicity problems. Its odor at low levels, to which a person may well adapt, and its irritancy at high concentrations appear to be limiting factors for continuous exposure in spacecraft. However, note the following Soviet results.

Mikhailov [55] studied the chronic toxicity of ammonia, a product of the activity of man, in experimental animals. At 7.2 to 8.1 mg/m^3 there seemed to be a cumulative action as expressed by increased organ/body weight ratios, decreased oxygen consumption, decreased weight gain, decreased lifespan.

There is little probability that occupants of spacecraft will experience chronic exposure to the strong irritant gases, HCl, HF, COF_2, SO_2, or NO_2, since they are usually formed only in emergencies. If such conditions should develop, the toxic effects would be chronic irritation of the respiratory tract which might cause bronchitis, tracheitis, pulmonary edema, or emphysema.

Methanethiol, CH_3SH, and other alkylmercaptans originate from feces and may be found at low levels in spacecraft. At these levels, odor control is the primary objective. Higher levels can have serious effects on the central nervous and circulatory systems [88].

Acetonitrile at high concentrations for acute exposures produces cyanosis. Chronic exposures at lower concentrations cause lesions in the brain, lung, liver, and kidneys [80]

p-Dichlorobenzene may be found as an offgassing product and thus presents a chronic exposure problem. It is a strong eye irritant and has been reported once to cause cataracts [6].

Carbon dioxide chronic exposures at about 2 or 3% by volume or greater produce a reversible, compensated acidosis characterized by increased bone deposition of carbonates. At levels below those producing respiratory stress there seems to be little, if any, effect on performance capability of submarine crews under these conditions [91].

Carbon monoxide by chronic exposure will reach an equilibrium level of hemoglobin saturation within 24 h or less in accordance with Coburn's equation [13]. There is evidence of compensatory increases of hematocrit and hemoglobin content of the red blood cells following prolonged, continuous exposures to carbon monoxide. If the burden of CO is great, the body's compensation can elevate the viscosity of the blood which may cause enlargement of the heart [52, 65, 106].

An extensive review was conducted by Soviet scientists on problems created by man's endogenous production of CO in a sealed environment. Considering the biochemical and physiological indices for man as affected by CO at 110 mg/m^3, they concluded that the minimum physiological shifts observed could not be due totally to carboxy hypoxemia, and that there was probably significant action by CO at the tissue level [46]. This is not unexpected considering that many tissues, such as muscle, contain other globin proteins having the tetrapyrrole moiety similar to hemoglobin.

Programs have been established to provide specific toxicologic information on selected propellants and to study the effects of long-term, continous exposure to possible trace contaminants at reduced atmospheric pressures and under the influence of one- and two-gas systems (oxygen or oxygen/nitrogen) [2, 66, 99]. These studies include definitive measurements of physiologic changes evidenced by clinical chemistry, changes in behavioral patterns, and gross and microscopic pathology, which, it is hoped, will permit more definitive evaluation of the space cabin problem.

Chronic effects on man have been noted as a result of the microbiological contamination of the AGA in closed systems. The indices of intellectual and physical ability to work deteriorated as microflora in the air increased and changed in composition [72]. In the flight simulation studies extending to 4 months by Borsenko, reduced responses of the central nervous sytem were noted accompanied by general suppression of activity and other physiologic functions such as resistance to the microflora [7].

Increased incidence of skin autoinfections was observed in submarine crews and flight simulation volunteers, which was attributed to nervous psychic fatigue and limited sanitary facilities [12]. The increased microfloral content of the AGA was also accompanied by reduced leucocytic phagocytosis and decreased lysozyme content of the saliva [70].

Possible use of algae (*Chlorella* sp) for converting CO_2 to O_2 led to a study of the effects of trace contaminants of the AGA on algal metabolism. Small amounts of ammonia, carbon monoxide, or acetone increased the average cellular consumption of CO_2. Hydrogen sulfide and air exhaled by man decreased the CO_2 utilization [44].

Combinations of Contaminants

Nearly all of man's encounters with contaminants in air involve more than one pollutant simultaneously. This is true in closed systems such as spacecraft and submarines as well as the open systems of occupational and public exposures. It is surprising to find very few studies on the toxicity of mixed contaminants; one reason may be the overwhelming number of possible combinations and permutations that might be investigated. It would be highly desirable to be able to predict with reasonable reliability whether the components of a mixture would act upon man independently, as oxygen and nitrogen, or interdependently. If they should act interdependently, would they be antagonistic, simply additive in their effects, or synergistic to produce a greater than additive effect? Even a plausible theory or hypothesis would be useful as a guide for choosing combinations for experimental study.

This problem has been discussed specifically in relation to space flight by Tiunov and Savateev [101], who suggest that mathematical equations can be developed for calculating the combined effects of contaminants in the AGA. It is necessary to know the kind of interaction between the components, if it is additive, antagonistic, or synergistic, in order to select the proper equation.

A mathematical approach to mixed gas exposures has been developed for occupational exposures by the Threshold Limit Values (TLV) committee under the chairmanship of Stokinger for the American Conference of Governmental Industrial Hygienists [3]. The mixture of gases and particulates from thermal decomposition of polymers has been analyzed and their acute toxicity determined [36, 99].

Experimental evaluation of the chronic toxicity effects of a mixture of gases was reported by Sandage [88]. The mixture consisted of hydrogen sulfide (20 ppm), methylmercaptan (50 ppm), indole (10.5 ppm), and skatole (3.5 ppm). Monkeys, rats, and mice were exposed continuously for 90 days. It is clear from their findings that the problem of mixed exposures is far from simple additivity. The observed effects were:

1. Sulfhemoglobin was formed to a significant degree in rats and monkeys, but ten times as much appeared in the blood of rats.
2. A low-grade hemolytic process appeared to exist in all animals, although there was no evidence of impairment of hematopoietic function.
3. There were marked species differences in response to the chemicals. Lung pathology was observed in 75% of the mice, but was not significant in the other

two species. Liver pathology was not significant in rats and monkeys but existed in 60% of the mice. Weight loss was significant only in the mice. On the other hand, stress tests revealed significant decrease in endurance of rats, but not of mice.

4. The real cause of death in monkeys is obscure. In mice and rats, however, the cause of death was probably anoxia and secondary respiratory infection, both of which are compatible with the lung pathology observed.
5. Rats and mice exposed to the mixture of compounds displayed a higher mortality rate than when exposed to the single compounds. There are a number of reasons for believing that this difference reflects significant differences among individuals with regard to sensitivity to toxic compounds. There is also evidence of adaptation to the toxic atmosphere if the animals are able to survive the first severe effect.

Data have been reported on the physiologic changes resulting from space flight. This study of actual manned space flights included the stress of weightlessness along with exposure to numerous contaminants of the AGA [25].

EXISTING AIR QUALITY STANDARDS

Individuals vary widely in responses to stresses by physical, physiologic and psychologic conditions. These variations, which occur among individuals and in any one individual from time to time, represent differences in genetic makeup and life history. Accordingly, the ideal method of avoiding excessive stress is to observe each person closely and to remove or limit the stresses when his response reaches an acceptable level, prior to that considered undesirable. The goal should be to develop standards for response limits rather than for stress limits. Unfortunately, knowledge of the multitude of response mechanisms in the human body is meager and means of observing them are quite limited, especially in spacecraft. It is expected that the Skylab experiments will provide data on this problem. The indirect approach must be taken to protect individual spacecraft occupants by limiting stresses, using engineering methods designed to maintain conditions that will not produce adverse responses in the *average human*. Variations from the average human are wide, making it necessary to incorporate safety factors when setting standards for design and operation of the engineering systems involved. This requires monitoring the health of each individual in space for changes.

Occupational Standards

One of the most comprehensive sets of standards (and best known) for safe exposures to air contaminants is the Threshold Limit Values (TLV) [3]. These standards for occupational exposures to more than 500 compounds "represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect." Other guidelines are available to the space toxicologist—the maximal allowable concentrations of the American Standards Association's Z–37 Committee [105]. Soviet toxic hazard standards for industrial exposure have been published [75, 107]. Much of the toxicologic basis for their standards is in a series of publications, the most recent of which is by Letavet and Sanotskiy [49a].

It has been suggested that these occupational values used for exposures of 8 h/d, 5 d/wk might be converted into values for continuous exposure in space. However, experience with submarines capable of continuous submersion up to 90 d has shown the necessity to reevaluate the data used for TLVs to establish safe air concentrations of the submarine air contaminants [11, 93]. Animal toxicity studies comparing 90-day continuous exposures with intermittent exposures of 8 h/d, 5 d/wk for 90 days at the TLV showed that the mathematical extrapolation of the TLV was most dangerous [88]. These tests in animals during 90 days at the Threshold Limit showed effects ranging from no mortality or other untoward effects to moderate toxicity, to almost complete lethality.

In our present state of knowledge it can be concluded that none of the industrial air limits can be used with certainty, either directly or by extrapolation, for space cabin environments. Although such an extrapolating equation has been proposed [97] in which all variables likely to affect toxicity were included, subsequent experimental animal work [99] showed that such a procedure could not be relied on in any given case. Unpredictable variations in the rate of metabolism under conditions of continuous exposure relative to intermittent exposure appear to be overriding. It should be noted that animal studies are not capable of revealing the magnitude of several of the factors included in any extrapolation equation [34]. Soviet and US scientists have independently reached the same decision [101].

Public Health Standards

Worldwide concern for environmental pollution has prompted many countries to develop air quality standards. Such standards are set in the US by the Environmental Protection Agency and by various States to protect the most sensitive segments of the population including infants and the aged. The standards incorporate large safety factors. A careful selection for spacecraft personnel, including excellent health, makes it clear that public air standards are not necessarily applicable to spacecraft AGA.

Submarine Standards

Experience in submarines, especially those capable of continuous operation for up to 90 days, is useful for spacecraft operation. Applicability to spacecraft of standards currently in use by the US Navy (shown in Table 2 [103, 104]) has been discussed by committees of the US National Academy of Sciences (NAS) [63, 66]. Even the 90-day exposure limits set for submarines are not directly applicable to spacecraft because of many differences [11, 97]. Efforts to use these values when mixtures of toxic materials are involved (which is almost always in aerospace situations) are not only meaningless but also may be dangerous.

Submarine standards give values for 1 h, 24 h, and 90 d. Standards for shorter times—ceiling values which should not be exceeded without risk of significant health effects—are designed to be applied to emergencies. Such limits represent the maximum allowable concentrations permissible under operational conditions and are not to be construed as permissible limits for repeated short-term exposures. It is envisioned that sufficient time between these peak exposures will have elapsed to allow complete recovery of the exposed individuals. In some cases, there may be minor symptomatology.

Spacecraft Standards

Preliminary recommendations of limits in space to the above compounds for 1 h, 24 h, 90 d, and 1000 d have been given for a few of the compounds in Table 2 [63, 66]. Summary tables of the toxic mechanism of these compounds, sites of attack on the body, and groupings in regard to

TABLE 2.—*Limits for Atmospheric Constituents in Nuclear Submarines*
(Limits in ppm by volume unless otherwise noted) (After [104])

Chemical substance	90-Day limit	24-Hour limit	1-Hour emergency exposure limit	Remarks
1. Acetone	300	2000	(*)	
2. Acetylene	6000	6000	6000	Set at approximately 1/4 of lower explosive limit of 2 1/2%
3. Acrolein	(*)	(*)	(*)	
4. Ammonia	25	50	400	
5. Arsine	0.01	0.1	(*)	
6. Benzene	1.0	100	(*)	See item 15 (a)
7. Carbon dioxide	3.8 mm Hg	7.6 mm Hg	19 mm Hg	Equivalent to 1/2, 1, and 2 1/2% at 760 mm Hg

TABLE 2.—*Limits for Atmospheric Constituents in Nuclear Submarines*—(Continued)
(Limits in ppm by volume unless otherwise noted) (After [104])

Chemical substance	90-Day limit	24-Hour limit	1-Hour emergency exposure limit	Remarks
8. Carbon monoxide	25	200	200	
9. Chlorine	0.1	1.0	(*)	
10. Dichlorodifluoromethane (Refrigerant 12)	200	1000	2000	Set by decomposition products formed in $CO\text{-}H_2$ burner
11. Dichlorotetrafluoroethane (Refrigerant 114)	200	1000	2000	Set by decomposition products formed in $CO\text{-}H_2$ burner
12. Ethanol	100	500	(*)	
13. Formaldehyde	(*)	(*)	(*)	
14. Freon refrigerants	–	–	–	See items 10, 11, and 37
15. Hydrocarbon solvents				Principal sources include: paint thinner, lighter fluid, mineral spirits, etc
(a) Benzene	3 mg/m³	3 mg/m³	(*)	Equivalent concentrations in ppm are listed under item 6
(b) Total aromatics (less benzene)	10 mg/m³	(*)	(*)	
(c) Total aliphatics (less methane)	60 mg/m³	(*)	(*)	
16. Hydrogen	10 000	10 000	10 000	Set at approximately ¼ of lower combustible limit of 4%[1]
17. Hydrogen chloride	1.0	4.0	10	
18. Hydrogen fluoride	0.1	1.0	8	
19. Hydrogen sulfide	(*)	(*)	50	
20. 2-Propanol	50	200	(*)	
21. Mercury	0.01 mg/m³	2.0 mg/m³	(*)	
22. Methane	13 000	13 000	13 000	Set at approximately ¼ lower explosive limits of 5.3%
23. Methanol	10	200	(*)	
24. Methylchloroform (1,1,1-trichloroethane)	2.5	10	25	Based on decomposition in $CO\text{-}H_2$ burner
25. Monoethanolamine (MEA)	0.5	3.0	50	
26. Nitrogen dioxide	0.5	1.0	10	
27. Oxygen	140–160 mm Hg not exceeding 21% by volume	140–160 mm Hg not exceeding 21% by volume	(*)	Physiological lower limit, fire safety upper limit
28. Ozone	0.02	0.1	1.0	
29. Paint thinner	–	–	–	See hydrocarbon solvents, item 15
30. Phosgene	0.05	0.1	1.0	
31. Phosphine	(*)	(*)	(*)	
32. Stibine	0.01	0.05	(*)	
33. Sulfur dioxide	1.0	5.0	10	
34. Triaryl phosphate	1.0 mg/m³	50 mg/m³	(*)	
35. 1,1,1-trichloroethane	–	–	–	See item 24
36. Trichloroethylene	(*)	(*)	(*)	
37. Trichloromonofluoromethane (Refrigerant 11)	5	20	50	
38. Vinylidene chloride	2.0	10	25	

*Limit has not been established.

[1] During battery charges, the H_2 limit shown above may be exceeded as discussed in Chapter 62, NAVSHIPS Technical Manual 0901–000–0020.

sources and chemical classifications have also been published [16].

The latest recommendations for air standards in spacecraft are given in Table 3 [63]. Similar to the submarine standards, the short-term limits are designed to allow time to cope with emergencies and represent ceiling values. If the limits are exceeded, alternatives must be considered such as wearing full space suits, masks, and helmets or opening the craft to discharge the contaminated air, or there may be significant health effects beyond minor discomfort anticipated at certain emergency exposure limits. These limits are based on the principles developed by the National Academy of Sciences-National Research Council (NAS–NRC) Committee on Toxicology for establishing emergency inhalation limits for military and space chemicals [95]. These principles were reviewed and expanded in 1968 by a NAS committee chaired by Nelson [66]. The committee utilized these criteria for trace contaminant control in manned spacecraft:

1. Contaminants must not produce significant adverse changes in the physiological, biochemical, or mental stability of the crew.
2. The spacecraft environment must not contribute to a performance decrement of the crew that will endanger mission objectives.
3. The spacecraft environment must not interfere with physical or biological experiments nor with medical monitoring.

In utilizing those criteria for development standards, these premises were adopted:

1. Any contamination of the spacecraft atmosphere *may* be detrimental.
2. Zero contamination level of the spacecraft atmosphere is impossible.
3. Data do not exist that will permit one to predict with precision the maximum contaminant concentration that will not cause degradation of the mission.
4. Provisional limit values can be established from some contaminants to serve as guidelines for design, development, and testing of future space systems.
5. These provisional limit values can ultimately be transformed into fixed limits if sufficient data about the effects of continuous exposure to a single compound and to multiple compounds can be obtained.

Of the 200 to 300 materials identified in hermetically sealed systems, the Committee selected 11 for immediate consideration and provisional recommendations. For purposes of these provisional criteria, the Committee assumed a spacecraft atmosphere ranging from 760 to 258 mm Hg total pressure, containing nitrogen as a diluent gas, oxygen sufficient to maintain normal (sea-level equivalent) alveolar partial pressure, and carbon dioxide below 5 mm Hg. Temperature and relative humidity are expected to be within the comfort zone for the total pressure selected. A detailed discussion is included in the report of the information studied for each substance. The shortcomings of the data and the needs for research are also discussed, which have since been reviewed and expanded by another NAS committee under the chairmanship of Stokinger. Spacecraft air quality standards were recommended for 52 compounds at these exposure times: 10 min, 60 min, 90 d, and 60 mo [63]. The compounds and recommended concentrations in the AGA are shown in Table 3 on the following three pages.

Soviet scientists have a similar approach to developing standards for spacecraft AGA. Gazenko and Genin considered the possibility of using submarine experience and recommended establishment of maximum levels for all harmful impurities in spacecraft [24]. Kuznegov recommended that pure oxygen atmosphere at 193 mm is dangerous, that a mixed gas should be used [47]. Nefedov and others called attention to interactions among spacecraft occupants, and to physiologic changes in occupants from this interaction [72].

Standards for contaminants were suggested by Gorodinskii, Levinskii, and Serbakov for 24-h continuous exposures [32]. Lebedinskii, Levinskii, and Nefedov suggested maximum values for more than 4 months' space flight [49], which are shown in Table 4.

TABLE 3.—*Atmospheric Contaminant Limits for Manned Spacecraft*
ppm (mg/m^3) (After [63])

Compound (molecular weight)	10 Min, special area[8]	60 Min	90 Days	6 Months	Footnotes
Alcohols					
1. Methyl alcohol	— —	200	40	40	
(32.04)	— —	(260)	(52)	(52)	
2. Ethyl alcohol	2000	2000	50	50	(6)
(46.07)	(3800)	(3800)	(95)	(95)	
3. n-Butyl alcohol	— —	200	40	40	
(74.12)	— —	(600)	(120)	(120)	
4. Isobutyl alcohol	— —	200	40	40	
(74.12)	— —	(600)	(120)	(120)	
5. sec-Butyl alcohol	— —	200	40	40	
(74.12)	— —	(600)	(120)	(120)	
6. tert-Butyl alcohol	— —	200	40	40	
(74.12)	— —	(600)	(120)	(120)	
7. n-Propyl alcohol	— —	200	40	40	
(60.11)	— —	(500)	(100)	(100)	
8. Isopropyl alcohol	400	200	40	40	
(60.11)	(1000)	(500)	(100)	(100)	
Esters					
9. Methyl acetate	— —	200	40	40	
(74.0)	— —	(600)	(120)	(120)	
10. Ethyl acetate	— —	300	50	50	
(88.10)	— —	(1080)	(180)	(180)	
11. Butyl acetate	— —	200	40	40	
(116.16)	— —	(940)	(188)	(188)	
12. Propyl acetate	— —	200	40	40	
(102.1)	— —	(840)	(168)	(168)	
Ketones					
13. Acetone	— —	1000	300	300	(6)
(58.08)	— —	(2400)	(720)	(720)	
14. Methylethylketone	— —	100	20	20	
(72.1)	— —	(290)	(58)	(58)	
15. Methylisobutylketone	— —	100	20	20	
(100.08)	— —	(410)	(82)	(82)	
16. Methylisopropylketone	— —	*100	*20	*20	(5)
(86.77)	— —	(350)	(70)	(70)	
Aldehydes					
17. Acetaldehyde	— —	50	10	10	(1)
(44.05)	— —	(90)	(18)	(18)	
18. Acrolein	— —	0.2	0.1	0.1	
(56.06)	— —	(0.5)	(0.2)	(0.2)	
19. Formaldehyde	— —	1.0	0.1	0.1	
(30.03)	— —	(1.0)	(0.1)	(0.1)	

See footnotes at end of table.

TABLE 3.—*Atmospheric Contaminant Limits for Manned Spacecraft*—(continued)
ppm (mg/m³) (After [63])

Compound (molecular weight)	10 Min, special area[8]	60 Min	90 Days	6 Months	Footnotes
Alicyclics					
20. Cyclohexane	— —	300	60	60	
(82.14)	— —	(1020)	(204)	(204)	
21. Cyclopentane	— —	300	60	60	
(70.13)	— —	(870)	(174)	(174)	
22. Methylcyclohexane	— —	500	*15	*15	(5)
(98.14)	— —	(2000)	(60)	(60)	
23. Methylcyclopentane	— —	300	*15	*15	(5)
(84.1)	— —	(1029)	(51)	(51)	
Halogenated aliphatics					
24. Chloroform	— —	100	5	5	
(119.39)	— —	(490)	(24.5)	(24.5)	
25. 1,2-Dichloroethane	— —	200	10	10	
(98.97)	— —	(800)	(40)	(40)	
26. Dichloromethane	— —	100	25	25	
(85.94)	— —	(340)	(87.5)	(87.5)	
27. Methylchloroform	— —	300	50	50	
(133.4)	— —	(1620)	(270)	(270)	
28. Tetrachloroethylene	— —	100	5	5	
(165.85)	— —	(680)	(34)	(34)	
29. R-11. Trichlorofluoromethane	— —	5000	100	100	
(140.5)	— —	(28 500)	(570)	(570)	
30. R-12. Dichlorodifluoromethane	— —	5000	100	100	
(124.0)	— —	(25 500)	(510)	(510)	
31. R-113. Trichlorotrifluoroethane	— —	500	50	50	
(192.5)	— —	(3950)	(395)	(395)	
Aromatics					
32. Benzene	— —	100	1.0	1.0	
(78.11)	— —	(320)	(3)	(3)	
33. Ethylbenzene	— —	200	20	20	(4)
(106.16)	— —	(860)	(86)	(86)	
34. Styrene	— —	50	*10	*10	(5)
(104.1)	— —	(215)	(43)	(43)	
35. Toluene	— —	200	20	20	
(92.1)	— —	(760)	(76)	(76)	
36. 1,3,5-Trimethylbenzene	— —	25	*3	*3	
(120.2)	— —	(123)	(15)	(15)	
37. Xylene(o-, m-, p-)	— —	100	20	20	
(106.12)	— —	(430)	(86)	(86)	
Halogenated aromatics					
38. Dichlorobenzene, (mixed o- and p-)	— —	50	5	5	
(147.01)	— —	(300)	(30)	(30)	

See footnotes at end of table.

TABLE 3.—*Atmospheric Contaminant Limits for Manned Spacecraft*—(continued) ppm (mg/m³) (After [63])

Compound (molecular weight)	10 Min, special area[8]	60 Min	90 Days	6 Months	Footnotes
		Heterocyclics			
39. 1,4-Dioxane	— —	100	5	5	(7)
(88.0)	— —	(360)	(18)	(18)	
40. Furan	— —	2	0.04	0.04	
(68.07)	— —	(5)	(0.1)	(0.1)	
41. Indole	1.0	1.0	0.1	0.1	(5)
(68.07)	(4.8)	(4.8)	0.5	0.5	(partially).
42. Skatole	1.0	1.0	0.1	0.1	(4)
(131.1)	(5)	(5)	(0.5)	(0.5)	(partially).
		Inorganics			
43. Ammonia	100	100	25	25	
(17.03)	(70)	(70)	(17.5)	(17.5)	
44. Carbon dioxide	40 000	30 000	10 000	10 000	
(44.01)	(72 000)	(54 000)	(18 000)	(18 000)	
45. Carbon monoxide	— —	125	15	15	(2, 3)
(28.01)	— —	(144)	(17)	(17)	
46. Hydrogen chloride gas	— —	5.0	1.0	1.0	
(36.46)	— —	(7.5)	(1.5)	(1.5)	
47. Hydrogen fluoride gas	— —	5.0	0.1	0.1	
(20.0)	— —	(4)	(0.08)	(0.08)	
48. Nitrogen dioxide	— —	2.0	0.5	0.5	
(46.01)	— —	(4)	(1.0)	(1.0)	
49. Phosgene	— —	0.5	0.05	0.05	
(98.92)	— —	(2.0)	(0.2)	(0.2)	
50. Sulfur dioxide	— —	5.0	1.0	1.0	
(64.1)	— —	(13)	(3)	(3)	
		Miscellaneous			
51. Acetonitrile	— —	40	4.0	4.0	
(41.05)	— —	(68)	(6.8)	(6.8)	
52. Methylmercaptan	1.0	1.0	0.1	0.1	(4)
(48.11)	(2)	(2)	(0.2)	(0.2)	(partially).

[1] Based on eye irritation.

[2] The 60-min limit is based on requirement that the carboxyhemoglobin level not exceed 10%, assuming heavy work activity (30 l/min respiration) and conformity to Coburn's equation. If the assumption of heavy work activity in the weightless situation proves unreal, then a value of 300 ppm (330 mg/m³) is recommended.

[3] The mg/m³ limits are also specified for the 70% O_2, 30% N_2 atmosphere at 5 psia (1/3 ATA).

[4] Long-term limits based principally on odor.

[5] Estimated levels bear an asterisk; more inhalation data with animal models would be desirable.

[6] Not to be included in group limits.

[7] These levels for dioxane are subject to drastic revision downward (< 1 ppm) if future research proves that the compound is carcinogenic in animal models at low (< 100 ppm) inhalation concentrations.

[8] 10 Min, special area. A proposed separate compartment in long-term spacecraft which has a higher ventilation and air purification rate than the rest of the craft. It will house the commode and may also be used for procedures involving air contaminants such as degreasing prior to soldering.

TABLE 4.—*Suggested Spacecraft Air Standards* (After [32, 49])

Contaminant	Duration	Standard
SO_2	24 h	1.5%
NH_3	24 h	5 mg/m^3
Total organic oxygen demand	24 h	150 mg O_2/m^3 in air
CO	24 h	15 mg/m^3
CO	>4 mo	5 mg/m^3
CO_2	>4 mo	0.2–0.3%

Khalturin and coworkers noted that water condensed from the AGA is a source for drinking and food preparation, and pointed out that almost all trace impurities in air are in greater concentrations in the condensation moisture [41]. Also, the microflora of the AGA possibly could chemically contaminate the water supply. If there is unavoidable microbial contamination of water supplies, organic halogen compounds may be used for sterilization [53]. Optimum concentrations of the agents and modes of dispensing depend on the level of reducing agents present along with the bacteria and thus require empirical study for specific spacecraft application.

This effect of trace contaminants in the air on the water quality of spacecraft calls for mention of recent recommendations by a NAS panel under the chairmanship of Housewright [62, 64]. They suggest quality standards for potable water and for wash water to be used for personal hygiene, which are in Tables 5 and 6.

CRITERIA FOR ADDITIONAL SPACECRAFT AIR STANDARDS

It is clear from the foregoing that air quality standards for trace contaminants in sealed environments must be developed with due regard to the specific system under consideration. The dual interaction between components of the system and the AGA must always be kept in mind. The air standards affect the choice of materials and systems just as the materials and systems selected affect the standards developed and the cost of meeting the standards. These considerations have been amply discussed here, and in the literature [46].

The principles and criteria from which the actual standards are developed are perhaps best described by those effects that are excluded or avoided. Unacceptable effects are: (1) any permanent adverse health effects; (2) any effects, even temporary, impairing the ability of the individual to carry out assigned tasks; and (3) any effects that will interfere with the purpose of the mission. Special circumstances must also be considered:

(a) Some degree of tolerance might develop in the course of prolonged space flights.
(b) Elements of additional hazard might be imposed on man by changes in the new generation of red blood cells formed after the first 90 days which could lead to potentially altered levels of susceptibility to toxicants.
(c) Increased sensitivity of specific tissues might develop, for example, in bone marrow, liver, and kidney, through changes in the subcellular components such as metabolizing enzymes which normally permit changes in response to environmental burdens.
(d) Restriction of movement and fatigue may add further stressful conditions to the environment and alter to a degree, as yet unknown, the response to toxic agents in humans [76].
(e) The effects of 5 psia, 100% oxygen may be profound, especially on those agents which can destroy the antioxidant defenses [2, 85]. As an example, reduction in levels of tocopherol in the plasma of Gemini astronauts has been reported along with a hemolytic process. There is some indication that in animals, oxygen at 5 psia will synergize with systemic toxic agents such as CCl_4 [99]. Species differences are quite marked, the primates being relatively resistant. The synergistic factors for specific agents in humans is still not known.

This rigorous approach for personnel safety is also consistent with scientific requirements. The NASA Space Medicine Advisory Group and the Respiratory Physiology Group of the NAS Space Science Board's 1966 Summer Study have

TABLE 5.—*Physical Standards For Potable Water in Spacecraft* (After [64])

Physical property	90 Days	6 Months	3 Years
1. Turbidity (Jackson unit) not to exceed	10	5	5
2. Color (platinum-cobalt units) not to exceed	15	15	15
3. Taste	Unobjectionable	Unobjectionable	Unobjectionable
4. Odor	Unobjectionable	Unobjectionable	Unobjectionable
5. Foaming (allowable persistence in s)	15	5	5
6. pH	– –	7.0 to 8.0	7.0 to 8.0

Proposed Permissible Limits for Inorganic Chemical Agents (mg/l or ppm) for Potable Water in Spacecraft

Agent	Mission Duration		
	90 Days	6 Months	3 Years
Ammonium	ns [1]	5.0	5.0
Arsenic	0.5	0.5	0.1
Barium	2.0	1.0	1.0
Bismuth	ns [1]	0.05	0.01
Boron	5.0	1.0	1.0
Cadmium	0.05	0.01	0.01
Chloride	450	250	250
COD (dichromate method)	100	100	100
Chromium (hexavalent)	0.05	0.1	0.05
Cobalt	ns [1]	0.02	0.01
Copper	3.0	1.0	1.0
Fluoride	2.0	2.0	2.0
Lead	0.2	0.05	0.05
Manganese	ns [1]	0.1	0.05
Iron	ns [1]	1.0	0.3
Mercury (alkyl)	ns [1]	0.005	0.005
Mercury (other)	ns [1]	0.05	0.01
Nickel	ns [1]	0.1	0.05
Nitrate (as N)	10.0	10.0	10.0
Nitrite	10.0	0.1	0.1
Selenium	0.05	0.05	0.01
Silica	ns [1]	10.0	10.0
Silver	0.5	0.1	0.05
Sulfate	250	250	250
Solids (Total)	1000	500	500
Zinc	ns [1]	5.0	5.0

[1] ns—No standard.

reaffirmed the principle that engineering exigencies should not dictate the environment; the environment must be supplied to provide the best medium for the experimental effort and it might also be added, the best medium for the mission profile. Thus, if one of the goals of prolonged manned space flight is to ascertain man's adaptability and response to the weightless environment, it is necessary to design manned spacecraft so that the Earth atmosphere or a reasonable simulation be provided in order not to prejudice the study of the one facet of space flight that cannot be duplicated on Earth—weightlessness [29].

TABLE 6.—*Tentative Standards for Wash Water Specifications* (After [62])

Physical/chemical/ microbiological standards	Specification
Color	≦ 15 cobalt units
Conductivity (specific, 25°C)	≦ 2000 μmho/cm
Foaming	Nonpersistent above 15s
Odor	Nonobjectionable
Carbon (total organic)	≦ 200 mg/l
Lactic acid	≦ 50 mg/l
Nitrogen (ammonia)	≦ 5.0 mg/l
Sodium chloride	≦ 1000 mg/l
Solids (dissolved, after evaporation, 180°C).	≦ 1500 mg/l
Urea	≦ 50 mg/l
Detergents	Not specified
Oxygen (demand, chemical)	Not specified
pH	5.0 (min.), 7.5 (max.)
Microorganisms (standard 48-h plate)	≦ 10/ml

The first step in recommending an acceptable concentration for exposure to an atmospheric contaminant is to describe the dose-response relationship. What effects will result from exposure to various concentrations for various periods? Such descriptions of exposure versus effects are sometimes called air quality criteria. In theory, with sufficient experimentation they can be determined quite precisely. In practice, at any given moment, use must be made of information available from a review of the literature, published and unpublished, even though not completely adequate.

The second step in recommending a concentration for human exposure to an atmospheric contaminant is to determine the acceptable level of effect which can then be matched against the dose-response curve to establish the concentration. The acceptable level of effect is almost completely dependent upon the circumstances of exposure. Will the exposure occur while strolling down the street? (In this case an objectionable odor might be limiting.) Or will it occur during armed combat? (In this case reversible hypertension might be acceptable, but temporarily decreased visual or auditory acuity would not.)

Let us consider briefly how others have defined an acceptable effect and proceed to what might be acceptable for 100- and 1000-day space flights. Then we will return to the first step of dose-response relationship and discuss some of the critical variables [108].

There is a wide spectrum of acceptable effects from air contaminants. At one extreme, Emergency Exposure Limits are recommended by the NAS Committee on Toxicology [95] or by an American Industrial Hygiene Association committee [38]. Both committees accept any reversible effect that (a) will not interfere with the performance of tasks to be accomplished during the emergency, (b) not significantly reduce vision or visibility or interfere with breathing or prevent self-rescue, and (c) not expose the individual to additional risks such as fire and explosion.

At the other end of the spectrum, criteria and standards are being developed to protect the public from adverse effects of air pollution, which require identification of the most sensitive segment of the population. Standards are then set at levels low enough to protect those sensitive individuals. Some of the principles involved have been discussed by a committee of the National Academy of Sciences [61].

When developing standards for specific circumstances of human exposure to toxic materials, a fundamental principle must be carefully observed:

> The *toxicity* of a substance is its intrinsic capacity to produce injury when tested by itself. The *hazard* of a substance is the likelihood it will produce injury under the circumstances of exposure [15].

Thomas [98] has classified the chemical toxicants that may be encountered in spacecraft into four categories according to the probable responses to low-level continuous exposure: (1) equilibrium (intake-excretion): (2) adaptation, desensitization, cross-tolerance; (3) cumulative damage; and (4) all or none (carcinogens, sensitizers).

A final factor must be included in criteria for developing AGA standards—the concern about the *total* health of the spacecraft occupants. We are not only looking at the health hazards of airborne materials but also all hazards regardless of route of entry. The total body burden must be considered when setting air limits for those materials which might also be ingested in food, water, or medication, or absorbed through the skin. The concern for total health of the individual in space again implies that each must be his own normal base for comparison for monitoring the effects of the spacecraft contaminants. A thorough preflight determination of each individual's physiology, metabolism, and reactions to stresses of various kinds is needed to make sure that an adequate margin of safety has been used in setting a standard [49].

It has been suggested that two numerical standards might be set for each contaminant. One would be an "alert" standard that would require intensive monitoring and perhaps special control procedures. The second would be an "abort" level requiring drastic action.

The recommendations for alert and abort levels and TLV_{space} in the classifications of Cox [16] and Hine [35] must still be looked on with some skepticism, because of the complexity of variables already discussed. The well-documented rationale by Hine is a good source for basic data; the concept was put into practice in a 90-day flight simulation in 1970 [79].

Committees such as those which have been discussed usually find the available data not entirely adequate for recommending standards, so that safety factors must be used. These safety factors should be of a magnitude commensurate with (1) the severity of the response; (2) degree of hypersusceptibility related to preexisting (such as respiratory) disease, heredity, and nutritional state; (3) extent of physical exertion; and (4) uniqueness of man's response, e.g. hypersensitivity of the respiratory tract [61]. Microbial infestation of spacecraft will be an increasing problem as the duration of flight and number of occupants increase. This will be reflected primarily in the quantity and quality of microflora on astronauts' skin and clothing. Particular concern is expressed for proliferation of fungi and yeast (*Candida* sp) which may be pathogenic to man [7]. The difficulty in treating diseases caused by such organisms further enhances the need for concern. The possibility cannot be excluded of microbes existing in the extreme conditions of space and planets. These microorganisms may be pathogenic for man, thus represent danger not only for crewmembers but also for the Earth's population upon return of the craft and equipment [7]. There is also considerable value in averting the uncontrolled drift of Earth types of life into space.

It is not easy to develop efficient methods of antisepsis for these various aspects of microbial growth. The methods selected must not have a negative influence on crewmembers in the complex medium of spacecraft. The methods must be compatible with the numerous and varied mechanical systems of space flight, be fire- and explosion-proof, and of minimum weight, volume, and energy requirements [7].

Therefore, the use of antimicrobial methods developed for other types of hermetically sealed rooms is not possible, especially when considering the possibility that microflora from cosmic space and other planets may be adapted to exist in extreme conditions, and thus may not be sensitive to such factors as ultraviolet radiation, vacuum, and high or low temperatures [7].

If resorting to chemical means for controlling the microflora, two other potential problems arise. The chemicals, such as phenol, may be a health hazard to the occupants, or the microorganisms may develop strains resistant to the chemical controls, which has occurred with hexachlorophene. Extensive research, development, and evaluation for new control methods are clearly needed.

Emergency Standards

In addition to the concerns already discussed, to be included in criteria for chemical and microbial contaminants during normal space flight, there must also be criteria developed for emergency situations, in order that they can be prevented, reduced in severity, or planned to be taken care of adequately when they do occur.

As Gazenko and Genin [24] have pointed out, it is necessary to consider the possibilities of emergency situations in space flight when maintenance of the optimum parameters of AGA will not be possible. These emergencies can be grouped as—medical, thermal, mechanical, and

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chemical—quite aside from those emergencies affecting the operation of the spaceship. They will require a high tolerance from man for several kinds of divergences from the optimum parameters.

Medical emergencies would include organ malfunctions, infectious diseases, dental problems, and similar. The medical significance and treatment of emergencies to the respiratory tract, skin, and eye from particulates in space cabins have been reviewed [9]. Other medical emergencies are beyond the scope of this chapter. Similarly, the physiologic emergencies—loss of control of heat or humidity in the craft and mechanical trauma and anoxia associated with partial or total loss of pressure—are beyond the scope of the present discussion.

Chemical emergencies which might arise from equipment failure require development of criteria and principles for control. A NAS panel chaired by Smyth [95] developed a basis for establishing emergency inhalation exposure limits applicable to space chemicals. The emergency limits for these compounds contain no safety factor and are considered tolerable for a single emergency during the duration of the mission.

These principles have been utilized for subsequent development of Emergency Exposure Limits (EELs) for specific compounds under specific conditions of exposure, which are listed in Table 7. It must be noted that none of these carries any safety factor and therefore they should *not* be applied to situations differing significantly from those for which they were developed. Potential new applications should be referred to the Committee on Toxicology of the US National Academy of Sciences in Washington, D.C.

The Emergency Exposure Limit for short-term exposure to an airborne contaminant is a concentration which, when inhaled for a specified single brief period (rare in an individual's lifetime), is believed not to result in a period of disability or interfere with the performance of his assigned task. In no event shall the value so selected produce danger from flammability of combustible aerosols, or result in substantial impairment of vision or visibility, or the ability to breathe. Transient effects may be experienced. The limits are intended to guide the informed specialist. It is believed that he can be more competent in protecting people if he is furnished

TABLE 7.—*EELs Recommended by NAS/NRC Committee on Toxicology* (After [95])

Compound	Time		
	10 Min	30 Min	60 Min
Acrolein	—	—	0.2 ppm
Aluminum fluoride	25 mg/m³	10 mg/m³	7 mg/m³
Aluminum oxide	50 mg/m³	25 mg/m³	15 mg/m³
Ammonia (anhydrous)	500 ppm	300 ppm	300 ppm
Boron trifluoride	10	5	2
Bromine pentafluoride [1]	3	1.5	0.5
Carbon disulfide	200	100	50
Carbon monoxide:			
(normal activity)	1500	800	400
(mental acuity)	1000	500	200
Chlorine pentafluoride [1]	3	1.5	0.5
Chlorine trifluoride	7	3	1
Diborane	10	5	2
1,1-Dimethylhydrazine	100	50	30
Ethylene oxide	650	400	250
Fluorine	15	10	5
Formaldehyde [1]	—	—	3
Hydrazine	30	20	10
Hydrogen chloride	30	20	10
Hydrogen fluoride	20	10	8
Hydrogen sulfide	200	100	50
JP–5 Fuel [1]	5 mg/l	5 mg/l	2.5 mg/l
Monomethylhydrazine (MMH)	90 ppm	30 ppm	15 ppm
Nitrogen dioxide	30	20	10
Oxygen difluoride	0.5	0.2	0.1
Perchloryl fluoride	50	20	10
Sodium hydroxide	4 mg/m³	4 mg/m³	2 mg/m³
Sulfur dioxide	30	20	10
Sulfuric acid	5 mg/m³	2 mg/m³	1 mg/m³
Tellurium hexafluoride	1 ppm	0.4 ppm	0.2 ppm
1,1,2-Trichloro-1,2,2-trifluoroethane (Refrigerant 113)	—	—	1500 ppm
Unsymmetrical dimethylhydrazine	100	50	30

[1] Tentative.

with a limit which, in the best judgment of a group of toxicologists, is the greatest concentration justified by the experimental evidence, provided the absence of any arbitrary safety factor is made known generally. This realistic limit would be analogous to the strength of material data used by the structural engineer in designing. The safety factor is applied in his operation of design, in proportion to the precision with which stresses to be withstood are known to the designer.

Emergency Exposure Limits cannot be promulgated without adequate experimental toxicological studies. The minimum information required is:

1. Beyond reasonable doubt, the identity should be known of the most sensitive target organ or body system whose integrity is menaced by short inhalations of the substances, and at what level effects on this target are insignificant.
2. It is necessary to have time versus concentration response data extending in both directions beyond the time intervals for which limits are to be promulgated, and sufficient observations to verify complete reversibility of effect. Data on two species, one a nonrodent mammal, are recommended as absolute minimum.
3. Certain human exposure data for orientation purposes are essential in estimating the emergency limits. These data can be obtained experimentally or by careful observation of any accidental exposures during commercial development.

UNCERTAINTIES OF STANDARDS

The development and promulgation of any standards for human exposure to atmospheric toxicants is fraught with many uncertainties. It is the intention in this section to point out a number of these uncertainties to develop skeptical caution, and suggest fruitful lines for further investigation.

The use of data from animal testing for predicting the effects of a substance on humans carries several sources of uncertainty, which include:

(a) differences among individuals of the same animal species,
(b) differences among animal species,
(c) extrapolation of data from animals to humans,
(d) differences among humans,
(e) nonuniformity of the contaminated air masses in gas leaks.

Chemical toxicants are rarely present alone, although most toxicity studies use pure materials. The difficulty in evaluating the milieu of contaminants in a spacecraft is the interaction among the components which has been discussed. The interaction may be physical, such as in the adsorption of gases on solid particulates; it may be chemical, as in the poisoning of catalysts in life-support systems; it may be biologic, where the toxic effects are modified either in degree or nature, as it in thickening of the alveolar barrier by NO_2 [61].

The dynamics of the spacecraft AGA pressure and composition are reflected in changing body burdens of the contaminants. Cumulative effects at any one time in such a variable exposure history are most difficult to assess. In addition to the usual effects which may be predicted in the average individual, there are also the unusual responses of allergic sensitization, idiosyncratic reactions, and adaptive tolerance. Nutrition plays an important role and specific dietary deficiencies may modify susceptibility.

Interpretation of information derived from animal experiments requires mature, experienced, scientific judgment from a variety of professional disciplines. The evaluation should consider all the variables mentioned and more, including conditions under which the data were obtained and, in particular, their relevance to the conditions of human exposure. Were data from human exposures available, they might result in standards of considerable reliability. Obviously, reliable human information is preferred, and should be obtained and utilized whenever possible. The research needs appear to be almost endless.

In spite of all the foregoing problems and uncertainties, the scientific community may well be proud of the advice it has provided to the space engineers on matters of toxicity and health hazards. The successes of the Soviet and US manned space programs are testimony to the skill of the astronauts and their supporting scientists and engineers.

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