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MAN'S TOLERANCE TO TRACE CONTAMINANTS

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The experiments reported herein were conducted according to the "Guide for Laboratory Animal Facilities and Care," 1965 prepared by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences—National Research Council; the regulations and standards prepared by the Department of Agriculture; and Public Law 89-544, "Laboratory Animal Welfare Act," August 24, 1967.

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FOREWORD

This invited paper was presented at the Conference on Bioastronautics 14-18 August 1967 at the Virginia Polytechnic Institute, Blacksburg, Virginia, by Dr. Anthony A. Thomas, Director, Toxic Hazards Division, Biomedical Laboratory, 6570th Aerospace Medical Research Laboratories. The Conference was sponsored by a grant from the National Aeronautics and Space Administration and concerned itself primarily with prognostication of the biological problems and solution options that may arise as space flight technology advances, and mission duration increases from 100 to 1000 days.

This technical report has been reviewed and is approved.

ROBERT H. LANG, LT COL, USAF, MC
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ABSTRACT

Atmospheric contaminants in sealed cabins originate from a multitude of sources: off-gassing from cabin materials, production of contaminants by the life support system components, and the end products of human metabolism. The scope of the problem increases with progressing mission duration and can become the limiting factor for man's tolerance to extended space flight. Several important aspects must be considered: truly uninterrupted, continuous exposure, a combination of physiological stress from the use of artificial atmospheres and the chemical stress imposed by the trace contaminants, and the great potential of synergistic toxic effect by various constituents of the highly complex mixture of many contaminants. Superimposed on these factors are the other aggravating characteristics of prolonged space flight: logistics problems of life support and psychological effects of isolation on performance. Clearly, these factors must be weighed singly and in combination to allow safe design of future manned systems. Validation of human tolerance to trace contaminants can be accomplished by prolonged animal exposures coupled with mathematical model verification. Tradeoffs in life support system design can extend tolerance to contaminants and long range logistic tradeoffs should be considered by utilizing extraterrestrial resources for contaminant removal purposes.

In September 1958 at the First International Symposium on Submarine and Space Medicine, I was asked to present a paper on Threshold Limit Values for hydrocarbons and ozone in confined spaces. (1)†

Making prognostications for an absolutely unknown area, the only thing I could do was to become philosophical about the problem. At that time it was quite obvious that the duration of the space trip would be of prime importance in deciding how much of various contaminants a man could take through the inhalation route. Knowing that you can't make progress without sticking out your neck, I flatly stated that we would have no problem from chemical stress, assuming that everything goes well with the life support system, as long as the exposures are at a relatively slow rate and that the mission duration does not exceed two weeks. Based simply on a dose-effect relationship, I also suggested that in this two-week continuous exposure period, compensating for the 3-fold increased dose, (this coming from comparison with the 8-hour interrupted exposure experienced in industry), we could use the Industrial Threshold Limit Values (TLV) and would probably be safe with this, a three-fold safety factor for most compounds. To give myself a little leeway, I arbitrarily divided chemical toxicants into four categories. (Table 1)* Category I included all those agents which, at low concentrations, will equilibrate within the organism very quickly. If equilibrium is reached in a matter of hours, and at a level where physiological compensation is still effective, continuous exposure should be of little consequence. In Category II were included those materials to which a certain tolerance or adaptation can be developed. It was found, with many chemicals, that short exposures to relatively high concentrations can increase tolerance considerably up to several months duration. In Category III (which I thought was the largest group) I covered all materials which exhibit slow clearances or cumulative properties, and in this category I have included most of the hydrocarbons. And, finally, in Category IV, I was worried about materials which could be placed on an all-or-nothing basis. These are materials which are carcinogenic, or materials where even trace quantities could be hazardous for continuous exposure, however short the duration of such exposure might be. I had to make these predictions without the benefit of any experimental data.

The presentation taught me one lesson; simply, that we would have to start doing some continuous exposures in animals, in order to get some basis for our philosophy and either prove or disprove what I said. Following that meeting, we started doing research on continuous exposure, and, naturally doing it the easy way, exposing animals up to 90-day duration at atmospheric pressure air environment to various "typical" chemicals. (Table 2) These typical chemicals were propellants which could be aboard the spacecraft -- such as hydrazine, UDMH, nitrogen tetroxide, pentaborane -- and typical industrial chemicals for which

† Such numbers refer to references

* See appendixes for tables and figures

we have quite a bit of toxicity data, such as carbon tetrachloride and phenol -- and then some chemicals which are the end products of metabolic processes, such as indole, hydrogen sulfide, methyl mercaptan; and also, just to throw in a fancy trick, a mixture of indole, methyl mercaptan and skatole. These exposures were performed at the appropriate industrial TLV for each chemical, that is, the value which is thought to be harmless for daily eight hour exposure, five days per week, for at least 30 years duration, in an industrial situation. As expected, we found that this concentration was detrimental to the health of animals in many instances, causing nearly 100% mortality with some; notably, hydrazine, decaborane, and the mixture of indole, skatole and methyl mercaptan. It then looked like the basic assumption of dividing chemicals into major categories was right.

No sooner did we find this out than I was invited again to give a paper, this time at a Symposium on Toxicity in the Closed Ecological System, sponsored by the U.S. Navy and Lockheed Missile and Space Company in Palo Alto, California. (2) I had to talk on the Environmental Toxicity of Space Cabin Atmospheres. This was a little bit easier assignment because at least I had some concrete data to lean on.

I have pointed out that hydrazine, decaborane, and the mixture of indole, skatole, methyl mercaptan, and hydrogen sulfide appeared to produce strongly cumulative toxicity. Looking at the rate of mortality during the exposure (Table 3), you can see that the majority of deaths occurred during the first month, which clearly indicates that continuous exposure at the TLV concentration had an early and overwhelming toxic effect.

In my presentation, I also pointed out that all the experimental data (which we and the Navy had at that time) on continuous exposures were at ambient pressure, air environments; this was fine for the Navy, but it left a big gap in knowledge as far as toxic effects during altitude flights are concerned. Obviously, we would have to study these chemicals in the proper environment since the effect of 100% oxygen atmosphere, at 5 psia, might cause undesirable pulmonary reaction, and such a reaction could greatly reduce the tolerance to certain toxic agents. On the other hand, the rate of absorption of toxic gases and vapors may be retarded at lower pressures and lower the magnitude of the inhalatinn exposure.

Therefore, we designed an inhalation facility to study these atmospheric contaminants in a space cabin environment. (3) As of this date, we have had the opportunity to study continuous exposure to contaminants for 90-day durations, in space cabin atmospheres of 5-psia, 100% oxygen, and in 5-psia mixed gas atmospheres, such as 68% oxygen - 32% nitrogen. The results of these studies are published and I won't dwell on them in great detail. (To keep the information disseminated as fast as possible, we started to sponsor an Annual Conference on Atmospheric Contaminants in Closed Spaces in 1965.) If you read the proceedings of these past

three conferences (4,5,6) you will agree with me that we are far from knowing enough about continuous exposure, and far from knowing enough about the effects of space cabin atmospheres on continuous exposure to toxic chemicals. We have only scratched the surface so far. Our basic philosophy is sound, but there is much more to this research than meets the eye. One has not only to define tolerance and no-effect levels, but also to consider adaptation. And, last but not least, one must consider comfort levels, and levels which not only do not cause reversible pathology but also do not affect the performance of the crew.

To highlight our knowledge, as of now, we can say that we are still uncertain about the significance of physiological and morphological changes which we are observing with the basic atmospheres of 5-psia 100% oxygen, and 5-psia mixed gas without contaminants. We see changes, and we will have to decide whether they are adaptive in nature, or whether they are deleterious for very long exposures. Our longest exposures to space cabin atmospheres have not exceeded eight months. An eight-month exposure is a far cry from a 1000-day mission duration. We yet have to validate by animal experiments the 1000-day tolerance to the basic cabin atmospheres.

I. DEFINITION OF MAJOR PROBLEM AREAS

A. The Trace Contaminant Problem

To briefly review the sources of contaminant generation in a closed atmosphere, Table 4 summarizes four major sources of equal importance. Since I do not want to trespass on the subject of the following speaker, Dr. Ross, who will review contaminant sources in much greater detail, I will refer you to the excellent paper by Conkle (7) where he reviews the complex contaminant picture found in a space cabin simulator atmosphere in the manned and unmanned portions of a 27-day manned experiment. A total of 97 compounds were identified, out of which 21 compounds were noted only during the manned portion of the study. Most of these compounds have been found by us, also, in outgassing studies on space cabin materials, where individual materials are placed in a sealed atmosphere of ambient pressure air, on one hand, and 5-psia oxygen, on the other, for periods of 30, 60, and 90 days -- after which the atmosphere is removed through a cryogenic trapping system and analyzed for contaminants (8). Tables 5 through 10 clearly illustrate that the gas-off rates are not uniform, and that repeated gas-off studies on the same materials, subjected to three consecutive outgassing periods of 30 days each, do not result in a reduction of contaminant generation rates in many instances; or, if generation rates are reduced by such pretreatments, they still remain at a very significant level. Other salient points demonstrated in these tables are a substantial amount of carbon monoxide production and significant amounts of hydrocarbons in the qualitative composition of these mixtures.

Carbon monoxide thus is produced by cabin materials, and is also produced by man. The previously cited paper by Conkle reports a steady increase of carbon monoxide from 1 mg/m^3 to 25 mg/m^3 during the 27-day experiment. Obviously, we know that we will have a problem with exposure to carbon monoxide and hydrocarbons, if nothing else.

Cabin materials are usually classified as metallic and non-metallic components. At the present time, nobody seems to be worried about metallic components. Non-metallic cabin construction materials are very much varied and depend upon each system, but about 600 various materials have been identified so far. Research performed in the past four years has clearly shown that many of these construction materials will gas-out various volatile components at an accelerated rate in the reduced pressure of the cabin.

Another large group of contaminants is generated by life support equipment, functioning properly or malfunctioning. By processing the cabin air, many of the original contaminants will be changed, oxidized, reduced, hydrolyzed, pyrolyzed, etc. One should also keep in mind that, with this very complex mixture of gases or volatile contaminants, interaction between these in the atmosphere is not only likely, but a certainty. So, the final spectrum of species which will be found in a cabin under operational conditions might be quite different from those which we observe in bench-scale laboratory tests.

There are, in addition to these contaminants, many non-permanently incorporated materials in the cabin. There are large numbers of chemicals used during the construction and check-out process which can accidentally be turned loose in a life support system. Examples of this are materials such as mercury used for checking out and calibrating pressure gauges and many solvents and degreasers used in the final assembly process.

That accident can play havoc with equipment is well illustrated by a life support simulator mishap which was discussed by Mr. Ray Saunders at our Second Annual Conference. As usual, one malfunction can trigger a chain reaction of other malfunctions, resulting in a truly vicious circle, and, ultimately, in an acute health hazard to the crew. This has actually happened and led to abortion of a manned environmental system simulator mission. A catalytic hopcalite burner was used to purify the atmosphere from contaminants. During the actual manned trial, humidity increased in the chamber due to occupancy by people. This caused moisture from the atmosphere to condense in an aluminum canister containing sodium superoxide. Now, the vicious circle began. The moisture generated sodium hydroxide from the sodium superoxide. Sodium hydroxide generates hydrogen when in contact with aluminum. To get rid of the hydrogen, the crew increased the flow rate through the hopcalite burner to a faster rate than that specified hoping to burn off the excess. By increasing the flow rate, the temperature of

the catalytic bed dropped; it became inefficient in combusting organic materials in the atmosphere. The chamber had been cleaned prior to use with a relatively harmless solvent, trichloroethylene. Residual trichloroethylene vapors, passing through the catalytic bed at a low temperature, were incompletely combusted to dichloroacetylene, which produced a marked clinical sickness in the crew and resulted in mission abortion on the third day.

This experiment has typically relied on control by remote sampling equipment, trapping out samples from the life simulator which, after being collected, had to be carried to an analytical laboratory for testing. It was only many months later that some elegant detection work discovered the nature of the toxicant giving clinical illness to the crew. In a real flight situation, assuming a 1000-day mission, there is no leeway for such post facto diagnosis. When a crew is actually confronted with some troublesome contaminant, it will be their job to identify it as soon as possible. Without knowing the resulting toxic product, it would be very difficult to correct any abnormalities in the life support system function to make safe processing of contaminants possible. This, in turn, points out the need for onboard, continuous flow monitoring devices with great sensitivity, and great analytical specificity for identifying various atmospheric contaminants.

Another major source of atmospheric contaminants comes from the excreta of human occupants. At the last count, there were over 150 of these definitely identified by analytical data, although not from a functional cabin atmosphere. The actual positive identification of the various components is an immense problem, even under laboratory conditions here on earth. Many of the life simulator runs have been sampled for atmospheric contaminants and the samples have been sent out to various laboratories for analysis. Depending upon the instrumentation used, the type of column materials employed in gas chromatography, and the circumstances under which the sample was obtained, laboratory results have come up with widely disagreeing results. As a consequence of this low credibility of analytical data, many of the engineering personnel have felt that the toxicity problem is over-amplified. Their argument is based on the successful completion of manned missions so far. A word of caution is in order here. Talking about a 1000-day mission is basically different from the present flight experience of a week or two week duration. Logistics problems dictate that oxygen will have to be preserved, reprocessed, and leak rates will have to be tightened down to prevent the loss of oxygen.

B. The Problem of Exposure to Complex Mixtures

When man is exposed to a multitude of contaminants simultaneously, each component of this mixture, depending on its concentration, may or may not exert a physiological effect. Table 11 lists five major probabilities

of the ultimate outcome of response. The problem of exposure to mixtures is not new and has been encountered frequently in industrial hygiene control of toxic materials. The listing of Threshold Limit Values (9) devotes a special chapter to exposures to mixtures. To quote their philosophy, "when two or more hazardous substances are present, their combined effect, rather than that of either individually, should be given primary consideration. In the absence of information to the contrary, the effects of the different hazards should be considered as additive. That is, when the sum of the following fractions,

$$\frac{C_1}{T_1} + \frac{C_2}{T_2} \cdots \frac{C_n}{T_n}$$

exceeds unity, then the threshold limit of the mixture should be considered as being exceeded. C_1 indicates the observed atmospheric concentration, and T_1 the corresponding threshold limit. Exceptions to the above may be made when there is good reason to believe that the chief effects of the different harmful substances are not in fact additive, but independent, as when purely local effects on different organs of the body are produced by the various components of the mixture."

Thus, the burden of proof rests on the toxicologist, and all of you who are familiar with biological research will agree that proving experimentally that components in a highly complex mixture do <u>not</u> have additive effect is an almost impossible research task. To oversimplify this matter, let us take a theoretical situation where 100 contaminants are present in an atmosphere, and all of these contaminants happen to have the same TLV - 100 mg/m^3. According to the book, the equation can be balanced to unity only if each of these individual components is present at 1/100 of its TLV concentration; that is, 1 mg/m^3. This would imply, then, that any of the components known to be safe at 100-fold this concentration cannot be tolerated in a mixture if any of them is present at the TLV level.

Table 12 illustrates a case where there is positive proof of additive (anesthetic and narcotic) effects from hydrocarbons, ketones and alcohols. By having these present as a mixture, and each of them at below its TLV, a definite decrement in performance could exist.

C. <u>The Contaminant Buildup and Exposure Profile Problem</u>

In a sealed cabin with a nominal leak rate and a constant generation of contaminants, the buildup of contaminant concentration is quite rapid and can be expressed by the equation on Table 13. The main factors governing this buildup are the magnitude of contaminants generation rates (w), the size of the outboard leak (b), and the progress of time (t).

Another equation which is useful to us, and is illustrated in Table 14 defines the time required to reach 99% of the final equilibrium concentration under conditions discussed on the previous Table.

Using these two equations, and substituting some realistic values for effective volume of the atmosphere in a present day spacecraft, the proper pressure and temperature values, and an unrealistically low constant contaminant generation rate, Table 15 shows that with our present leak rate, which is approximately one pound per day, the contaminant concentration would equilibrate as soon as the 30th day of the mission at about 2 mg/m^3. If the contaminant should be a highly toxic material such as ozone, although it is generated in quantities not exceeding its TLV for a one day exposure, at the end of 30 days it would be present at 10-fold this concentration, and there would be severe lung irritation and death. We will be capable of 100-day missions in the coming years and we are projecting ourselves into the most distant future 1000-day mission area. Most likely, leak rates will have to be tightened for logistics reasons. Assuming the same parameters and the same very low contaminant generation rates, but a 10-fold decrease in leak rate, 0.1 pounds per day, the equilibration would occur at over 20 mg/m^3, which means that even a less toxic contaminant could present a serious health hazard.

Since nothing illustrates the point better than a good visual aid, Figure 1 recapitulates the rate of exposure of the crew, with the present 1 pound/day leak rate. It can be seen that even on a short 100-day trip, the crew will be exposed to a rapidly increasing concentration during the first 30 days and to a steady concentration during the remaining two-thirds of the trip. From a biological standpoint, if you consider the area under the curve as a measure of exposure, their exposure will be fairly constant for the entire mission duration. Of course, you could live with this situation for 1000 days if your final concentration stays below the limit of undesirable physiological response.

The exposure profile during the 1000 day mission, illustrated in Figure 2, assumes a 10-fold decrease in leak rates as a logistical necessity, and shows again, from a biological standpoint, that the exposure will be fairly uniform, as related to the area under the curve, because equilibrium will be reached within the first quarter of the mission duration. The great difference, however, is the 10-fold increase in the contaminant level, indicating that compounds of moderate toxicity can play a significant role in determining limiting factors for mission duration.

How serious this limitation can be becomes clear from Figure 3. This is a distribution graph of the toxicity of industrial chemicals which are listed in the compilation of Threshold Limit Values. For the sake of simplicity, they were categorized by TLV's falling into four major

ranges, from 0 to 1, from 1 to 25, from 25 to 100 mg/m^3, and those which are in excess of these values. Out of a total of approximately 370 materials, more than 50% are in the range of 0 to 25 mg/m^3, and these should be considered highly toxic. Almost two-thirds of these chemicals have a TLV not exceeding 100 mg/m^3. Notwithstanding that these are chemicals which had to be controlled in the industrial environment, there is a valid analogy to control problems in cabin atmospheres. An overwhelming proportion of our gas-off products from cabin materials are industrial chemicals, and the likelihood of a similar percentage of "bad actors" amongst all the gas-off products is not too remote. Thus, we can conclude that with a 1000-day mission, and a minimal leak rate, even moderately toxic products which must be assumed to have additive effects should be removed from the atmosphere.

D. The Prediction of Tolerance Problem

Prediction of tolerance to a single toxic compound alone is quite difficult. While some extrapolations can be made from existing animal exposure data and human tolerance, Haber's Law, i.e., concentration x time $^{(n)}$ = constant effect, works fine with limited time durations, but in long term continuous exposure, the value of the exponent 'n' is uncertain, and may vary from compound to compound, and with different lengths of exposure.

Introduction of mixtures to space cabin environments, together with the artificial atmospheres, causes further complications. At the previously cited Symposium on Toxicity in the Closed Ecological System, Dr. Herbert Stokinger, from USPHS, presented a paper entitled, "Validity and Hazards of Extrapolating Threshold Limit Values to Continuous Exposures." (2) In his paper, rightly so, he pointed out that all the environmental factors must be taken into consideration, and he introduced an equation (Table 16) which, using the basic TLV's and correcting for such changes in environment as the dosage factor from ambient pressure change to 5-psia pressure change, toxicity from continuous dosage, toxicity from temperature change, toxicity from restricted motion, toxicity due to 100% oxygen atmosphere, toxicity due to fatigue, and toxicity from interaction of all these factors, could possibly give an eyeball figure, or a target figure to be used in setting continuous exposure limits for submarines and spacecraft. While this is certainly a very attractive approach, the individual factors must be assigned numerical values if we want to solve this equation. More often than not, these values must be determined experimentally since there isn't much known about them. To further complicate the matter, many of the gas-off products which were identified in the analytical studies are not listed in the Threshold Limit Values list, but, by chemical structure, resemble some of their relatives which we can find in the listings. Toxicity information on these materials is non-existent and must be obtained by animal experimentation.

II. VALIDATION OF HUMAN TOLERANCE TO TRACE CONTAMINANTS FOR THE 1000 MISSION

Admittedly, the previously listed problem areas are serious and quite discouraging. The present state-of-the-art is centered around some experience with 90-day continuous exposure to certain toxic agents in ambient air environment and in single and mixed gas, 5-psia cabin atmospheres. Looking at the 1000-day mission, we are not yet certain that man could tolerate any of the 5-psia basic atmospheres for that duration. Much less can we speculate about tolerance to toxic chemicals in such artificial environments.

I am sure that many in our audience have seen a number of proposed compilations for tolerance criteria for various space missions. You might ask, "what is so difficult about setting these limits? Many people have set such limits already." I would say in answer to that: every toxicologist can set some limits with a reasonable approach, having a reasonable potential of success; just on the basis of intimate knowledge of toxicity of that chemical. However, even if his predictions are valid 999 times out of a 1000, the one instance where he missed may hurt the whole crew. So we are talking, really, in the case of these lists, about forecasts and educated guesses.

Suppose we should have to submit these values to an Approval Board which would ask: how valid is your estimate? It's not too far-fetched to say, then, that we can draw an analogy and say that establishing space Threshold Limit Values for man's tolerance to a contaminant during a 1000-day mission will require the same amount of experimentation, justification and documentation as required today for qualifying a new drug or a new food additive, or a new pesticide for use in the community. For example, in qualifying a new drug, the following questions are asked: What is the effect of the drug itself on the central nervous system? On the autonomic nervous system? On the cardiovascular system? On the respiratory system? And on the GI and excretory system? What is the effect on special senses? On taste, on smell, on auditory, or optic function? The composition of the blood?

The next big question asked is what is the effect of the new drug on the activity of other commonly used drugs? The duration of action or potency of selected common central nervous system depressants and excitants? The effect on the duration of blood levels or the rate of urinary excretion of common acidic or basic drugs? After all, we may have to use drugs during the flight! The effect upon the absorption of essential minerals and vitamins from the gastrointestinal tract? Obviously, these last questions are directed toward potentiation and synergistic effects. As far as the matter of qualifying a new pesticide is concerned, some other questions are also asked. What is the acute toxicity? What is the subacute toxicity? What is the chronic toxicity?

A subacute toxicity study is a 90-day study, in this instance. In the chronic study, the time of elapsed observation is two years. Serial sacrifices, of course, are required during this period, at 6, 12, and 18 month intervals. During the whole experimental period, each animal is considered as an individual, and observations are made of every change that affects the individual. You have to take into consideration the dietary effects on the toxicity of that chemical (just as we should take into consideration the effects of an artificial atmosphere). You have to observe satisfactory growth and longevity. You have to know the target organs, and you have to know the mode of action. You have to know the intermediary metabolism, you have to know any adaptive processes going on - such as drug metabolizing enzymes, etc. Of course, you also have to do reproduction studies and paired-feeding studies.

After all this experimentation is completed, it must prove conclusively that whatever pesticide residue remains on foodstuff is a negligible quantity. "Negligible residue" for pesticides has been recently defined by the Food and Drug Administration as, "any amount of a pesticide remaining in or on a raw agricultural product that would result in a daily intake regarded as toxicologically insignificant on the basis of scientific judgment of adequate safety data. Ordinarily, this will add to the diet an amount which will be less than 1/2000 of the amount that has been demonstrated to have no effect from feeding studies on the most sensitive animal species tested."

Finally, after all this expensive research, the question is: how valid is your extrapolation to humans? I would like to quote Dr. Harry Hays, the former Director of the Advisory Center on Toxicology, from his speech at our First Annual Conference on Atmospheric Contamination in Closed Spaces, where he expounds on the problems of extrapolation and interpretation of animal data to man.

"The subject I have been asked to comment on is one on which, I think, can be found no general agreement. There are some, who feel that the risks involved in attempting to extrapolate animal data to man are too great, and that man himself must become the experimental animal. In order to set the stage for this discussion, I think a brief review of the evolution of animal experimentation and predictability of toxicity in man lends some justification for the pessimism that has prevailed on the value of animal studies.

"In the beginning, it was customary to use a rat or two, an odd rabbit, and a few mice. Before long, it was clear that toxicity in man could not be readily predicted in this way. So the number of rats increased, and before long, someone started statistics - so the number of rats increased still further. Dogs came in, rabbits went out. Cats became scarce. Well, predictions improved, but still there was a long way to go. So the number of rats increased again; so did the dogs; so did the mice. More species were added - monkeys, chimps,

marmosets, quail, frogs, and pigs. Longer tests were required: 10 days, 2 weeks, 6 months, 2 years, 1 whole lifespan. Still no closer to predictability in man. Once it was just toxicity, and then it was multi-generation tests. Carcinogens came in, and co-carcinogens; and if you couldn't find a carcinogen, you looked for a mutagen. If you couldn't find a mutagen, you looked for a teratogen. We used not one species, but many species. Not one strain, but many strains. Out-bred, in-bred, brother-sister mated, random mated. Still no better predictability. Once you counted just the dead. This procedure was charged with fallacy, so everything that could be weighed was weighed, and everything that could be removed was sliced and examined histologically. The function of every organ was looked into. From the cellular, we went to the sub-cellular. Radioisotopes became a must. Physiology gave way to psychology. And now, not even the rat doubts the results!"

This may sound humorous, but it's also a very serious and sad aspect in validating tolerance criteria for a 1000-day mission. Let's compare these things with our present experience. For example, eight months continuous exposure to 5-psia, 100% oxygen alone seems to be definitely toxic to the dog - practically no change in the monkey and in the rat. You may well ask, then, will man behave like the rat, like the dog, or like the monkey? We know now that the dog shows changes in eight months. The question is, will the other species show changes also, if you were to carry this exposure to 1000 days? And the ultimate question is, will man show any changes? And if he does, will we be astute enough to observe them? Will we look at subcellular morphology? Will we do punch biopsies after the flight? There might not be any gross clinical changes! Our animals did not show any abnormal clinical laboratory tests. To observe these changes, you have to look at the cellular level in the tissues. But this is exactly the requirement in qualifying a drug in animal toxicity tests - the cellular changes; the subcellular changes are the earliest indication of any effect, good or bad. You may well ask, then, even if you go through these animal studies, how do you extrapolate to man, ultimately?

Well, from many, many pharmacological studies leading to the qualification of a drug, taking the no-effect value in an animal, there are some average rule-of-thumb type extrapolations carried out from animal to man. It is always assumed that man is about six times as sensitive as the dog, 10 times as sensitive as the cat, 10 times as sensitive as the rat. Now, the next philosophical question is, will we take the no-effect level in animals and then put this six to 10 times safety factor on it? Or will we settle for a level which causes no irreversible pathology, coupled with no change in performance? This, obviously, is a decision which we will have to make. It is a decision that is both philosophical and mission oriented; and still, we must consider that man is not expendable.

Considering these great difficulties, it becomes fairly obvious that the chemical insult is something which perhaps could be spared the crew during the long mission. There are other insults which can not be avoided. The chemical insult could be avoided by engineering methods or by proper handling of the atmosphere; or, if it cannot be avoided, it should certainly be minimized to the greatest possible extent. We should never take the approach to engineer to a given tolerance limit and not do one better and try to get zero concentration of a particular contaminant in the atmosphere.

This, then, should be our general approach in developing man's tolerance to cabin contaminants. There is a great danger of being over-confident based on present experience in manned space flight. This over-confidence is multiplied by the apparent safety of nuclear submarine atmospheres. Table 17 points out the basic differences between submarine and space cabin environments which aggravate the atmospheric contamination problem during the long space mission. We should also remember that all these ventures are new, and that not enough time has elapsed yet to evaluate objectively the true occupational medicine significance of prolonged confinement to a closed atmosphere on the crew.

The same over-confidence in validity of data has resulted in many tragedies in the drug development area. I don't have to remind you that at one time we thought thalidomide was safe! Our margin for error is very small. In a 1000-day mission, the point of no return is reached quickly and dramatically. Choices for corrective action to control contaminants may be limited or only partially effective.

I want to apologize for disappointing those who have expected me to present a well-rounded list of man's tolerance to cabin trace contaminants. Since my guess probably wouldn't be any better than that of those who have tried it before, I thought I would be wasting your time. (Moreover, I didn't want to climb out on another limb this year as I have done in the past.) And last, but not least, such lists have the inherent capability of reappearing in several guidance documents as bibles and cure-all solutions for a "relatively simple" problem.

III. TRADE-OFFS IN EXTENDING HUMAN TOLERANCE TO TRACE CONTAMINANTS

By now it should be pretty clear to everyone that we are hamstrung by two major obstacles in the quantitation of human tolerance. The first one is in the area of experimental verification of tolerance and extrapolation of animal data to humans; the second is that even if we would have a better grip on man's tolerance to long-term exposure to trace contaminants, we probably would find in the process of our attempt to fully exploit his tolerance (whatever magnitude it might be) that we would be taking an unreasonable amount of calculated risk.

A. Trade-offs in Biological Research

How can we proceed relative to the toxicological studies on space cabin material and atmospheric contaminants in the cabin? Obviously, we are talking now about the biological research leadtime area, which is a real bottleneck. If we assume, as we did previously, that we will have to set some tolerance limits with a reasonable degree of validity and safety, we will have to do animal experimentation. Moreover, we will have to do this experimentation in the proper basic cabin atmosphere, which is characteristic of the mission. It's bad enough that we cannot simulate readily many of the other stresses present, such as weightlessness, psychological stress, and so on, although there are some hopeful signs of simulating psychological stress in animals by utilizing conflict techniques in performance measurements. Clearly, then, at the present state-of-the-art, if we would like to set fairly valid tolerance limits for a 1000-day mission, we would have no choice but to run the animal experimentation for at least the full 1000-day duration. Depending on our success at "picking" the "right" concentration (or dose) of the chemical at which we would run the experiment, we might find an effect level which is marginal, and then we would have to find the no-effect level. So, we are talking here of at least two or possibly three or four 1000-day runs.

Frankly, this is unrealistic, simply because the facilities for such volume of work in this country, or anywhere else in the world, are just not existent. Whatever capability we have now cannot be tied up indefinitely in 1000-day runs, because the rate of progress will be so slow as to be useless to the engineering people who are designing these systems. Clearly, the state-of-the-art needs rapid advancement. Presently, there is a great degree of uncertainty in the overall experimental approach to delineate the effects of multiple contaminants on the overall human tolerance, primarily because of the potential synergistic and additive effects. Predictive equations are needed which can extrapolate the integrated toxic effect of a certain concentration of a single toxic agent or a fixed concentration ratio of multiple toxic agents from a minimum duration animal exposure capable of causing typical chronic effects. Otherwise the medical authorities cannot predict the ultimate compounded summation of toxic damage with progressive increments of exposure time. Also, to avoid toxic effects, such equations should predict a reduced level of concentration which, for a certain length of exposure, although longer than that used in animal experiments, would be without adverse biological effects.

This clearly puts us into the area of mathematical model design. The equations previously discussed, if interrelated, are a good start. Careful analysis of animal experimental data, with the aid of regression equations and advanced probability statistics, applied to all of the criteria of toxicity (death, growth curves, laboratory data, gross and

histopathology findings, and the performance data from trained animals) will certainly lead to a dose-dependent proportional increase in the magnitude of the exponent power of time in Haber's Law. Once this relation of the exposure length to toxic effects has been defined mathematically, and verified experimentally over and over again, the model should be further widened by the inclusion of Stokinger's equation. This will require experimental verification of the upper and lower limits for each factor in the equation. Thus, the development of the mathematical model, aside from being the only tool to shorten the leadtime involved in the biological experimentation, will also eliminate the human error which is introduced by the judgment factor in assigning numerical values to a great number of "fudge" factors. On the basis of such a mathematical model, then, a computing device must be designed, first for test purposes to enable more economical and expedient planning of sequential and comparative toxicological exposure studies in the laboratory, and, ultimately, to be used in decision making on mission abort, should an unexpectedly high contaminant concentration develop during flight.

B. Trade-offs in Engineering Design

The greatest potential trade-offs are in the areas of life support system design. Moreover, these trade-offs are inherently more effective than biological trade-offs.

1. Testing of Life Support Systems

Since it is clear that we must make every effort to supply the purest possible atmosphere for our crew, this implies that our air purification equipment should be not only oversized but also redundant. Coupled with that, we must have a quick diagnostic capability for malfunctions and their effects on the constitution of atmospheric contaminants in the cabin.

Fortunately, malfunctions can be simulated and studied during the development cycle. Therefore, it is absolutely imperative that each life support system (with its complete assembly of subsystems) undergo a "mode of failure" analysis, which detects the implications of one malfunctioning subsystem on the functions of the other subsystems. This should be verified by experimental studies, during which complete information must be collected on atmospheric contaminant composition, both quantitatively and qualitatively. This is the only way that the crew will be able to predict the effect of various malfunctions during the trip and will be able to find the correct procedures for repair which will not result in the production of unknown or unexpected atmospheric contaminants.

2. Leak Rates

In the previous discussion, the effect of cabin atmosphere leak was demonstrated to have a major effect on equilibration time, level of equilibration of contaminants, and thus the overall exposure

profile of the crew. Figure 4 illustrates graphically the tremendous decrease of the contaminant problem as the leak rate is increased to 5 pounds per day, and the dramatic increase in contaminant concentrations as the leak rate is decreased to 1/10 pound per day. The trade-off in leak rates is a very attractive contaminant control procedure which can be designed into the system from the very beginning. It is a far more convenient and a safer procedure than a forced emergency measure of dumping the entire cabin atmosphere and repressurizing during the mission. This latter procedure, of course, requires interruption of the shirt-sleeve condition. Depending on the number of EVA's planned, an optimum cabin leak rate could be selected that would keep the contaminant concentrations low enough between depressurization periods. (It is questionable whether such complete vehicle depressurizations will be performed in the multi-compartment, sophisticated vehicles planned for the 1000-day mission.)

3. Filtering Devices

Filtering devices have two basic problems: (1) they all reach a saturation point and, to be useful on a long mission, they either must be replaced or regenerated. Figure 5 illustrates the contaminant concentration along the bed and the contaminant concentration on the atmosphere leaving the bed as time of the filter usage increases; (2) As the composition of the atmospheric contaminant mixture changes (and it will change during the mission), the lower boiling point materials which were generated at a slower rate from cabin materials will increase in concentration and will replace the more volatile materials from the filter bed, thus returning them to the cabin atmosphere. Regeneration of such filter beds, if feasible during such a long trip, must be performed with extreme care, so that contaminants stripped off from the filter do not re-enter the atmospheric circulation. Very likely, there are extra-terrestrial sources for absorbents for toxic chemicals. Many of the materials found on extraterrestrial bodies, which have been in vacuum, should be able to absorb quite a considerable quantity of gaseous or particulate contaminants. Processing such materials to increase surface adsorption characteristics and maximize absorbent capacity is within the state-of-the-art. Most likely, materials can be found which are of geological origin and can serve as trickling media or filtering beds for process vessel fillings. This would immensely aid our solid and liquid waste disposal.

4. Replenishment of Oxygen Supply and Power Sources

There is even distant hope that, by some process, water or oxygen can be extracted from extraterrestrial material. This would mean an increased atmospheric supply of fresh, uncontaminanted oxygen. Another area where extraterrestrial supplies could become useful is in power generation for the life support system. (Power is required to

operate our pumps, compressors, gas exchangers, and even our instrumentation.) It's entirely plausible that materials may be found which are combustible, or that materials could be found which may be directly used for batteries and fuel cells. And, one step further, the existence of radioactive materials has been frequently postulated. Even solar energy might be useful. Far-fetched as they may sound, enroute resupply might be the only solution to solve atmospheric contamination problems on a 1000-day mission when the point of no return has been reached.

C. Trade-offs in Human Tolerance in Emergencies

The final question of course is: Given a set of unfavorable circumstances and unforeseen problems, can we extend man's tolerance itself in an emergency situation? I think the most obvious and maybe partial solution to the problem would be to give man a break, remove him from the contaminated atmosphere to interrupt his continuous exposure. Perhaps this could be accomplished by supplying absolutely clean atmosphere for the duration of his rest and sleep cycles. Perhaps the crew quarters should be isolated into an operational and rest area, wherein a minimum volume of sleeping space, the atmosphere would be clean. Perhaps the airlock, after each EVA, with its fresh atmosphere, could be used for such a purpose. This would mean that we have interrupted the vicious circle of continuous exposure and reduced it to an exposure of 12 hours a day, rather than continuous 24 hours a day. With all the adaptive processes and repairability of the human body, such a break might be life-saving and might mean the difference between failure or success of the mission. Other ways to accomplish such abruption of continuous exposure would be to use gas masks, filters, oxygen masks, etc.

CONCLUSIONS

1. The state-of-the-art for predicting man's tolerance to trace contaminants for the 1000-day mission is not here. It must be developed in good time so that it will be present within the next 10 years. It will take an all-out effort from all of our scientific talent and from all of our research facilities. Suitable mathematical models of chronic toxicity during long-term continuous exposure must be developed for single and mixed contaminants to increase the prophetic value of animal experimentation and subsequent extrapolation to man.

2. Since we are dealing with unknown quantities, both in the toxicological stress and in the combined stress areas, our design philosophy must be that we will not impose a chemical health hazard by contamination of the cabin atmosphere.

3. We should set tolerance limits only for those contaminants which we can not eliminate by any method at our disposal, assuming a best effort on the part of our engineers. Examples for such contaminants may very well be carbon monoxide and volatile hydrocarbons.

4. If we are to set group tolerance limits for a multitude of similar contaminants (e.g., hydrocarbons), we should remember that we must assume that their toxic action is additive, unless we are willing to accept the burden of experimental proof to the contrary.

5. The types of limits which will be needed are (1) ceiling limits which are valid for the entire mission duration and (2) two types of emergency limits: the alert limit, which should have sufficient latitude in time duration so that maintenance and repair work can be accomplished without over-exposure, and an abort limit which is clearly applicable only within the initial phase of the mission.

6. Tolerance to trace contaminants should be studied in a combined stress environment. Mission equivalent length Bio-satellite Programs, where animals could be exposed in the atmosphere of an orbital station to actual contaminants in a cabin atmosphere simultaneously with all the combined stresses that cannot be simulated in our earth-bound laboratories, are highly desirable to advance our knowledge.

The state-of-the-art to maintain these animals by only periodic visits of scientists and technicians from earth is clearly here. Without this type of animal testing, any tolerance limit set for 1000-day missions will remain a highly speculative figure. If a separate program is not feasible, the manned orbital laboratories should consider animal complement to the crew. By leaving the animal population in orbit for substantially longer periods than the astronauts, valuable histopathological information could be developed on adaptive and incipient degenerative changes at the cellular level.

7. Life support system components, subsystems, and the integrated system should undergo a rigorous mode of failure analysis to avoid catastrophic toxic exposures as a result of malfunctioning equipment or the application of "stop-gap" type of emergency procedures and inflight modifications or servicing. The effect of proper and feasible corrective actions on the contaminant spectrum should be verified experimentally.

8. The study of the potential resources for life support systems in the extraterrestrial environment must be pursued. On the material resources side of the extraterrestrial environment lies the only hope for truly interplanetary missions and the exploration of the planets. Our best prediction is that on such missions, toxic manifestations from trace contaminants could become the true limiting factor to mission duration if resupply of oxygen and filtering media is impossible.

TABLE 1

PROBABLE RESPONSES TO
LOW LEVEL, CONTINUOUS EXPOSURE

I. Equilibrium (Intake = Excretion)

II. Adaptation, Desensitization, Cross-tolerance

III. Cumulative Damage ("Summation of Interest")

IV. "Non-or-all" (Carcinogens, sensitizers)

TABLE 2

SUMMARY OF MORTALITY RATES

COMPOUNDS	MONKEYS		RATS		MICE	
	NO DEAD / NO USED	% DEATHS	NO DEAD / NO USED	% DEATHS	NO DEAD / NO USED	% DEATHS
CONTROLS	1/10	10	0/50	0	1/100	1
N_2H_4	2/10	20	48/50	96	98/100	98
UDMH	1/10	10	3/50	6	6/100	6
DECABORANE	6/10	60	25/50	50	82/100	82
NO_2	0/10	0	9/50	18	13/100	13
CONTROLS	0/19	0	2/50	4	38/200	19
INDOLE	2/10	20	5/50	10	22/100	22
METHYL MERCAPTAN	4/10	40	5/50	10	43/100	43
H_2S	0/10	0	12/50	24	26/100	26
CCl_4	1/10	10	0/50	0	0/100	0
PHENOL	0/10	0	0/50	0	0/100	0
MIXTURE OF- INDOLE, H_2S, SKATOLE, Me•SH	16/20	80	32/50	64	99/100	99

TABLE 3

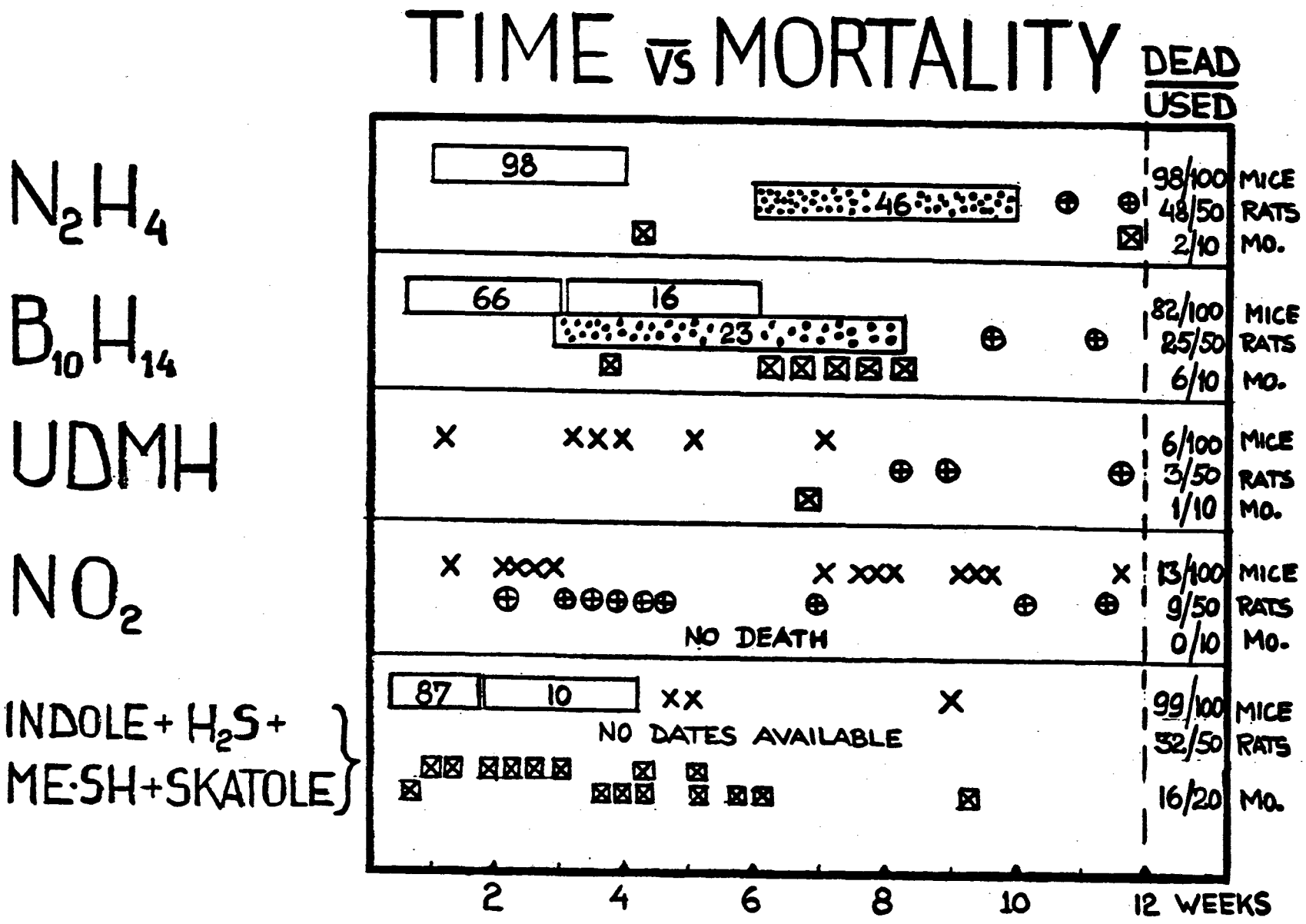

TIME VS MORTALITY
DEAD
USED
N_2H_4
98
46
98/100 MICE
48/50 RATS
2/10 MO.
$B_{10}H_{14}$
66
16
23
82/100 MICE
25/50 RATS
6/10 MO.
UDMH
6/100 MICE
3/50 RATS
1/10 MO.
NO_2
NO DEATH
13/100 MICE
9/50 RATS
0/10 MO.
INDOLE + H_2S +
ME·SH + SKATOLE
87
10
NO DATES AVAILABLE
99/100 MICE
32/50 RATS
16/20 MO.
2
4
6
8
10
12 WEEKS

TABLE 4

SOURCES OF CONTAMINANT GENERATION
IN CLOSED ATMOSPHERES

Man and His Activities

Materials and Outgassing

Equipment and Processes

Malfunctions and Emergencies

Table 5

GAS-OFF PRODUCTS - VELVET COATING NO. 104-C 10 BLACK

Storage Time (Days)	Atmosphere	Wt. of Component (Mg per 10 g Candidate Material)						
		Ethanol	Acetone	Methylethyl Ketone	Toluene	CO	Methane	Naphtha*
30	Air	0.3	0.1	0.4	0.02	2.8	0.04	1.0
60	"	0.3	0.3	0.5	0.02	3.6	0.06	1.0
90	"	0.1	0.1	0.4	0.02	4.5	0.10	1.0
30 + 30	"	0.05	0.1	0.3	0.02	0.7	N.D.	0.4
30 + 30 + 30	"	0.04	0.08	0.2	0.01	0.6	N.D.	0.4
30	5 psia Oxygen	0.4	0.5	0.3	0.2	4.9	0.16	1.0
60	"	0.2	0.1	0.6	0.02	4.0	0.08	1.0
90	"	0.08	0.3	0.5	0.01	5.4	0.12	1.0
30 + 30	"	0.09	0.09	0.3	0.02	1.2	N.D.	0.5
30 + 30 + 30	"	0.07	0.09	0.3	0.01	0.9	N.D.	0.4

*Estimated from group of GLC peaks characteristic of C_5-C_7 hydrocarbons.

Table 6

GAS-OFF PRODUCTS - CLASS H SILICONE IMPREGNATING VARNISH NO. 997

Storage Time (Days)	Atmosphere	Wt. of Component (mg per 10 g Candidate Material)					
		Ethanol	Propionaldehyde	Benzene	Toluene	Xylene	CO
30	Air	0.2	0.7	0.1	0.05	0.2	2.3
60	"	0.3	0.5	0.02	0.004	0.01	2.4
90	"	0.2	0.4	0.04	0.05	0.01	2.7
30 + 30	"	0.4	0.2	0.01	0.03	0.1	0.3
30 + 30 + 30	"	0.4	0.1	N.D.	N.D.	N.D.	0.2
30	5 psia Oxygen	0.04	0.5	0.02	0.2	0.3	2.0
60	"	0.05	0.2	0.02	0.5	0.2	2.6
90	"	0.05	0.4	0.02	0.9	0.7	2.9
30 + 30	"	0.03	0.1	0.02	0.6	1.0	0.7
30 + 30 + 30	"	0.04	0.2	0.04	0.7	2.0	0.5

Table 7

GAS-OFF PRODUCTS - 3614 GRAY COATING, XA-194

Storage Time (Days)	Atmopshere	Wt. of Component (mg per 10 g Candidate Material)					
		Ethanol	2-Propanol	Methyl Ethyl Ketone	Toluene	Xylene	Sat. Hydrocarbons
30	Air	1.5	1.1	0.4	7.1	2.9	0.3
60	"	1.4	0.7	0.7	13.5	13.4	1.1
90	"	1.0	0.3	0.3	7.6	13.8	0.4
30 + 30	"	1.1	0.8	0.5	12.1	5.8	0.5
30 + 30 + 30	"	0.6	0.5	0.3	8.1	4.2	0.2
	5 psia Oxygen						
30		3.7	3.0	0.9	12.2	5.7	0.6
60	"	0.8	0.9	0.3	6.3	5.7	0.4
90	"	0.6	0.7	N.D.	3.3	4.8	0.4
30 + 30	"	0.7	0.4	0.1	2.9	2.0	0.1
30 + 30 + 30	"	0.5	0.3	0.2	2.1	1.5	0.1

Table 8

GAS-OFF PRODUCTS - SILVER MARKING INK NO. 1448 (W/Cresylic Acid)

Storage Time (Days)	Atmosphere	Wt. of Component (mg per 10 g Candidate Material) 2-Ethoxy-Ethanol	2-Ethoxy Ethyl Acetate	Acetone	CO
30	Air	0.3	7.0	0.1	0.08
60	"	0.9	6.8	0.2	0.2
90	"	0.6	12.5	0.7	0.2
30 + 30	"	0.4	15.0	0.4	0.06
30 + 30 + 30	"	0.5	11.8	0.3	0.09
30	5 psia Oxygen	0.7	10.8	0.2	0.1
60	"	0.5	9.5	0.2	0.1
90	"	0.3	9.2	0.2	0.1
30 + 30	"	0.1	9.0	0.1	0.08
30 + 30 + 30	"	0.2	7.1	0.1	0.09

Table 9

GAS-OFF PRODUCTS - LATEX FOAM RUBBER

Storage Time (Days)	Atmosphere	Wt. of Component (mg per 10 g Candidate Material)	
		Carbonyl Sulfide	Carbon Disulfide
30	Air	0.03	0.002
60	"	0.05	0.002
90	"	0.09	0.004
30 + 30	"	0.03	0.001
30 + 30 + 30	"	0.04	0.001
30	5 psia Oxygen	0.07	0.002
60	"	0.10	0.002
90	"	0.12	0.004
30 + 30	"	0.12	0.002
30 + 30 + 30	"	0.13	0.002

Table 10

GAS-OFF PRODUCTS - SILICONE PRIMER, EC-1694

Storage Time (Days)	Atmosphere	Weight of Component (mg per 10 g Candidate Material)			
		Ethanol	n-Butanol	2-Propanol	Toluene
30	Air	4.6	14.2	26.4	2.7
60	"	4.6	6.5	29.6	3.4
90	"	8.2	10.0	18.9	7.9
30 + 30	"	1.8	15.5	15.3	0.7
30 + 30 + 30	"	0.4	13.8	8.3	0.1
30	5 psia Oxygen	4.1	11.1	21.7	3.3
60	"	4.6	10.4	27.9	4.2
90	"	7.2	12.6	25.4	6.5
30 + 30	"	2.3	10.7	14.8	2.9
30 + 30 + 30	"	0.8	9.6	10.5	1.1

Table 11

TOXICITY OF MIXTURES

Effects:

Independent
Potentiative
* Additive
Synergistic
Antagonistic

* TLV for ADDITIVE COMPONENTS:

$$\frac{C_1}{TLV_1} + \frac{C_2}{TLV_2} + \frac{C_3}{TLV_3} + \ldots \frac{C_n}{TLV_n} = 1.0$$

Table 12

ADDITIVE ANESTHETIC AND NARCOTIC EFFECTS FROM HYDROCARBONS, KETONES AND ALCOHOLS

	AIRBORNE CONC. (mg/m^3)	TLV (mg/m^3)
Butadiene	2000	2200
Ethyl Ether	1000	1200
Propane	1600	1800
Acetone	2200	2400
Ethyl Alcohol	1700	1900

$$\frac{2000}{2200} + \frac{1000}{1200} + \frac{1600}{1800} + \frac{2200}{2400} + \frac{1700}{1900} = 4.4$$

Table 13

CONTAMINANT BUILDUP IN SEALED CABINS

$$C_{(mg/m^3)} = \frac{w}{b}\left[1 - e^{\frac{-(bt)}{a}}\right]$$

where:

w = mg contaminant generated per day
b = m^3 atmosphere leaked per day at x psia
a = m^3 total effective gaseous volume of cabin
t = days elapsed time; e = 2.718

Table 14

TIME TO REACH 99% OF
EQUILIBRIUM CONCENTRATION

$$t_{days} = 4.6\,\frac{a}{b}$$

where:

a = m^3 total effective volume
b = m^3 leak per day at x psia

Table 15

TYPICAL CABIN VALUES

Effective Volume:	8.5 m^3 (300 ft^3)
Pressure:	253 mm Hg (5 psia)
Temperature:	26°C (78°F)
Contam. Generation:	0.26 $mg/m^3/day$*
Leak Rate:	1.0 to 0.1 lb/day

LEAK RATE (lb/day)	EQUILIBRATION Time	Conc.
1.0	30 days	2.1 mg/m^3
0.1	250 days	21.0 mg/m^3

*If Mol. wt. is 64: 0.26 mg/m^3 = 0.1 ppm

Table 16

PROPOSED EQUATION FOR ESTIMATING SPACE TLV's FROM INDUSTRIAL TLV's (Dr. Stokinger)

$$TLV_{space} = \frac{TLV_{ind} \times F_{press.}}{F_{cont.} \times F_{temp.} \times F_{decond.} \times F_{O_2 tox.} \times F_{fat} \times F_{interact.}}$$

where $F_{interact.} = f_1 \times f_2 \times f_3 \ldots\ldots \times f_n$

f_1 = 3 fold dose (8><24 hrs) excess toxicity

f_2 = additive toxicity of O_2

f_3 = fatigue + O_2 toxicity

Table 17

IMPORTANT FACTORS INFLUENCING ATMOSPHERIC CONTAMINATION

Aggravating	Beneficial
Continuous Generation and Exposure	Leak Rate of Cabin
* Reduced Pressure	Materials Selection
* Volume/Man Ratio	Preconditioning of Materials
* Power and Weight Limitation	
Filter Characteristics	
Complexity of Contaminants	
* Multi-Stress Environment	
* Escape Lead Time	

*Not significant in nuclear submarines

FIG. 1

CONTAMINANT PROFILE

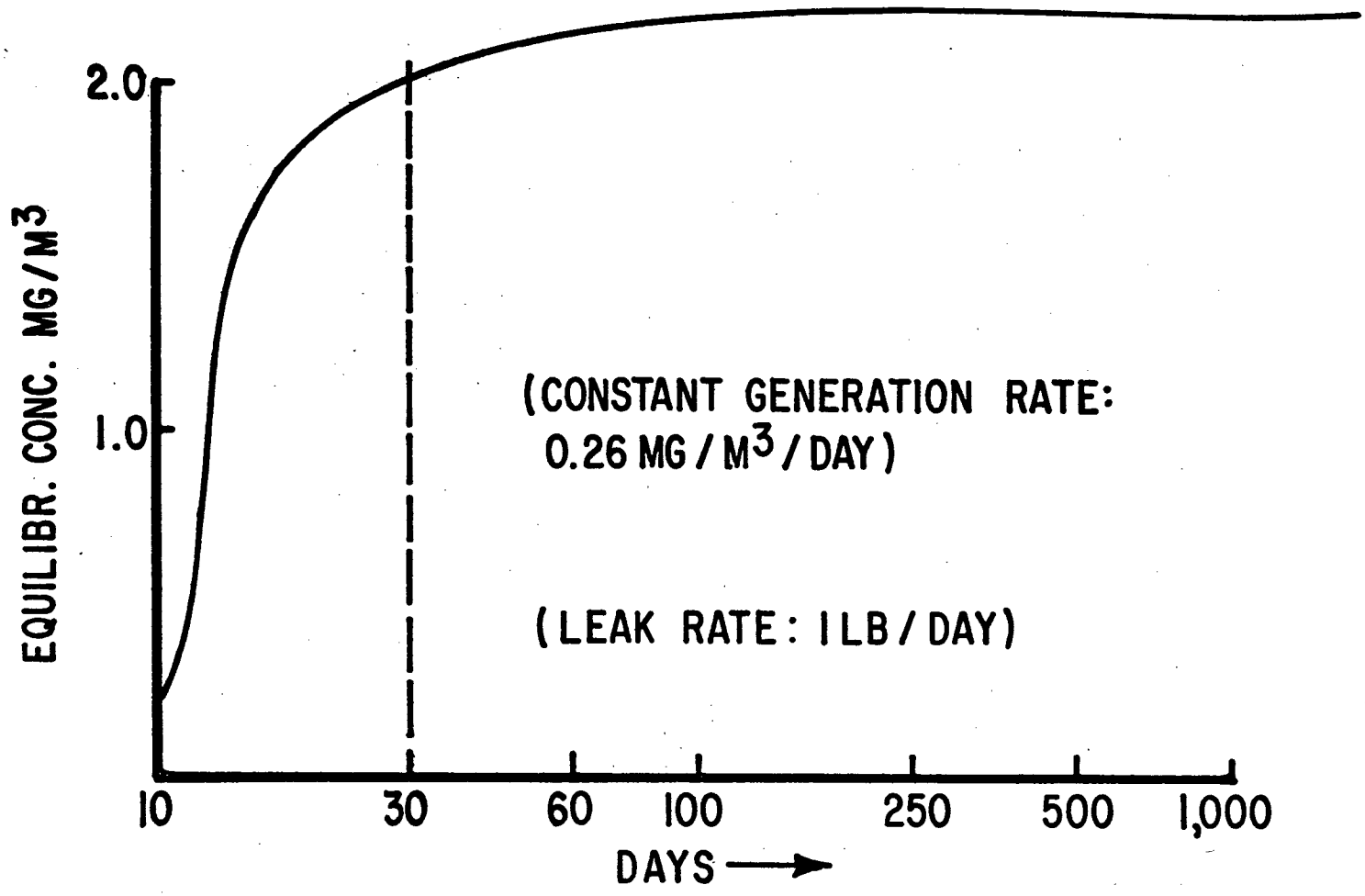


FIG. 2

CONTAMINANT PROFILE

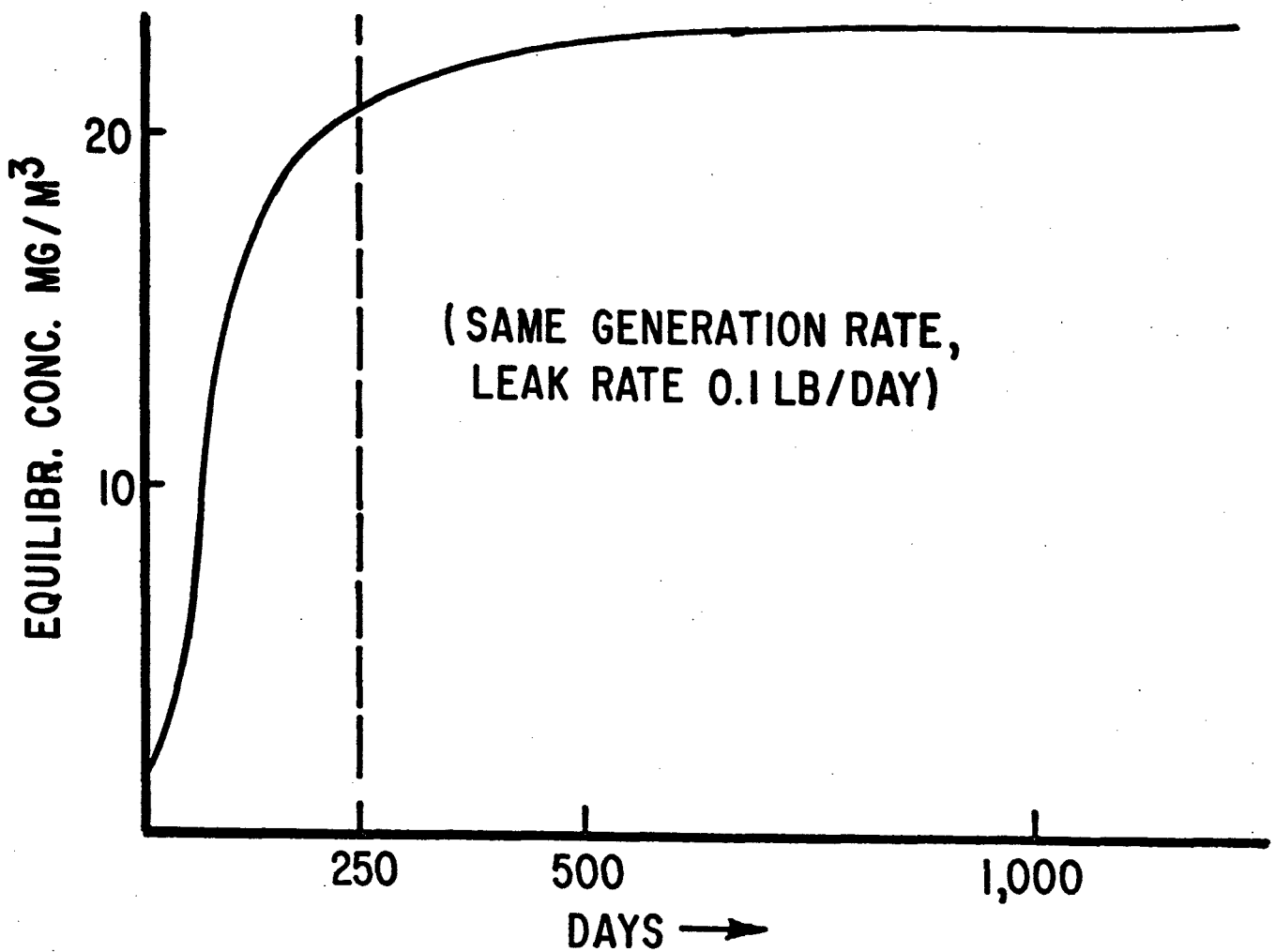
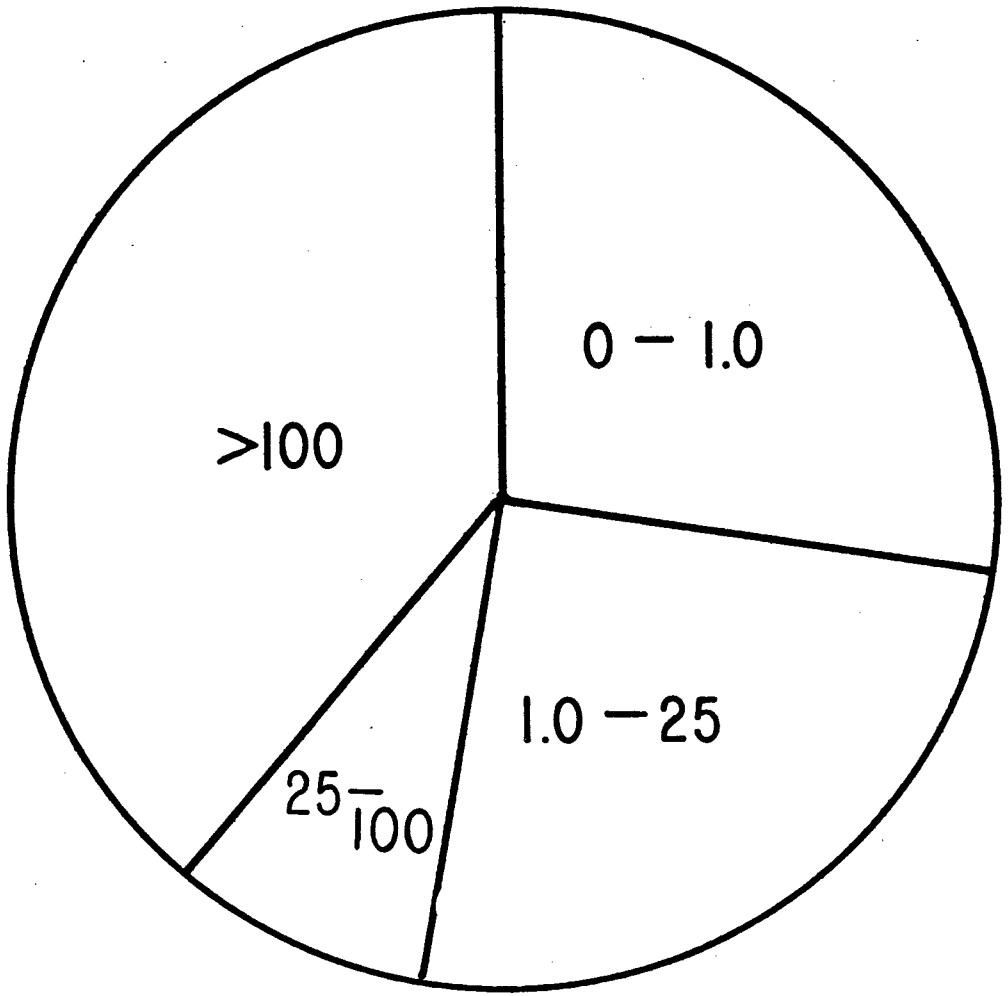


FIG. 3



DISTRIBUTION OF TLV-s
(MG/M^3)

Figure 4

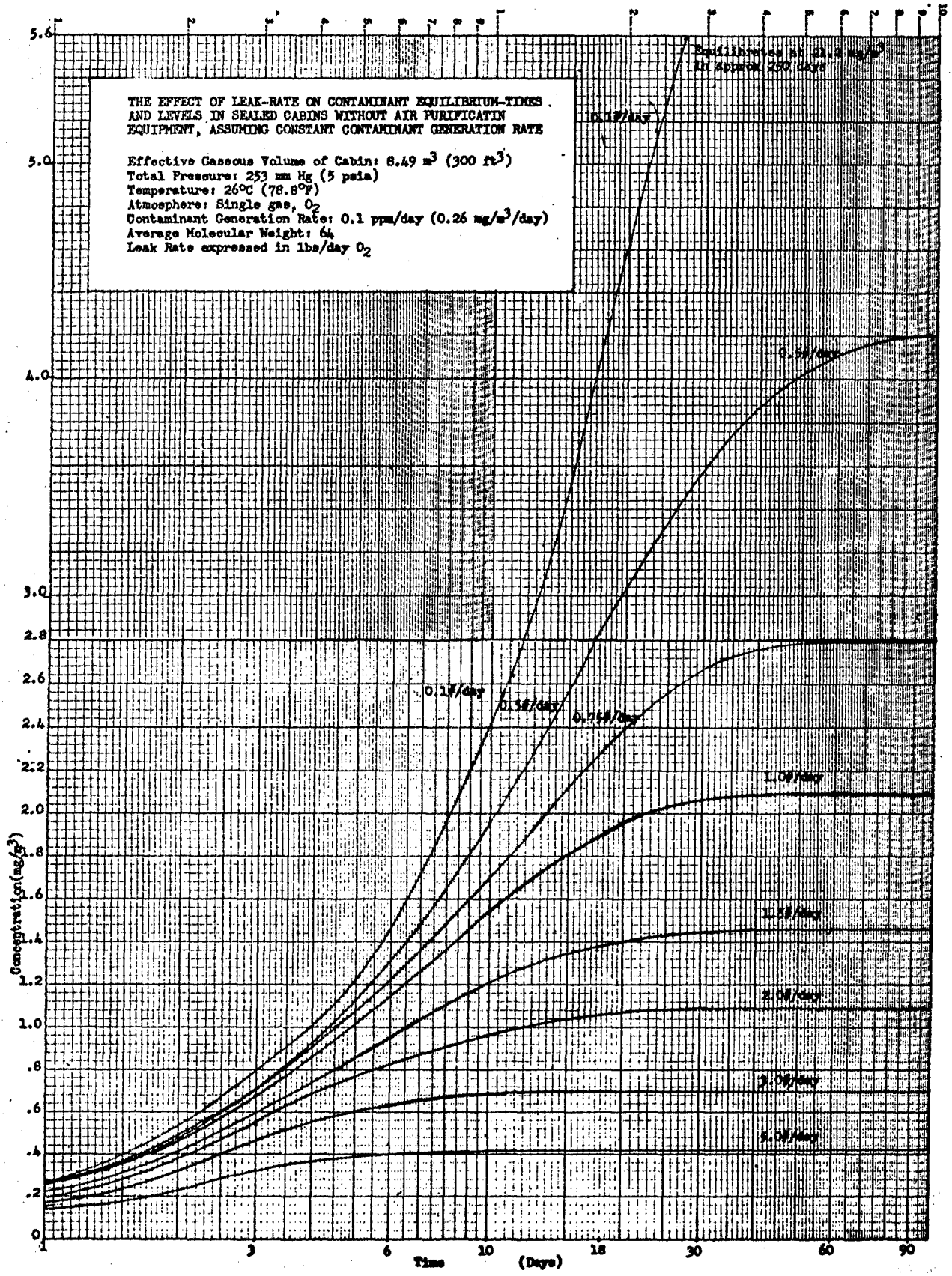
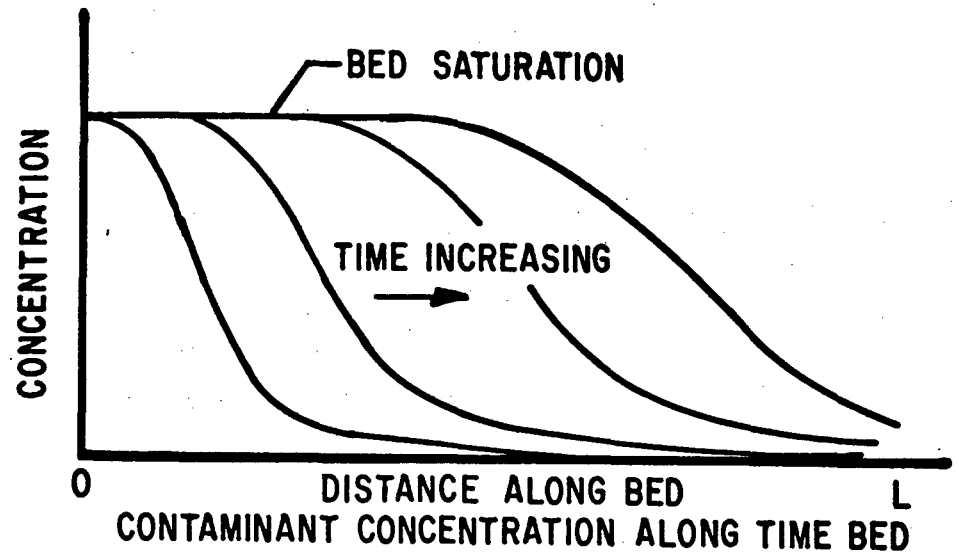
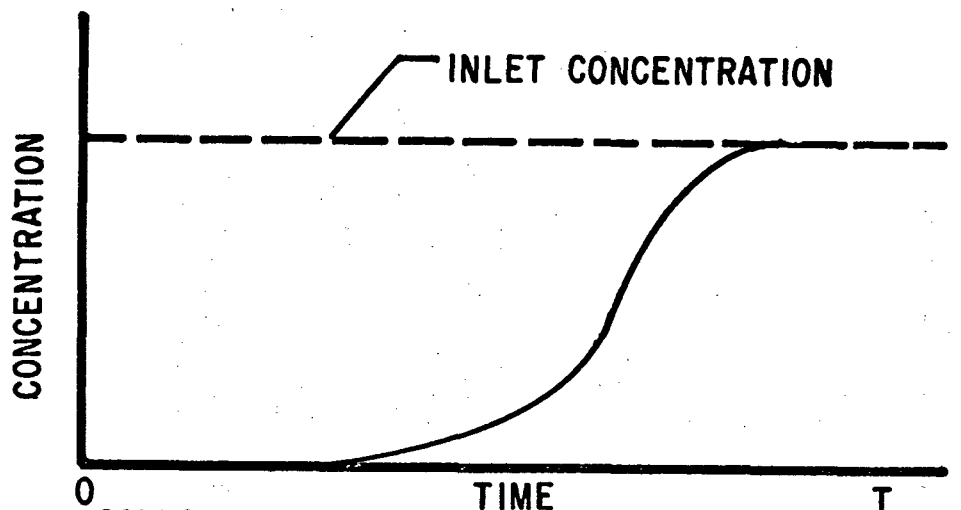

THE EFFECT OF LEAK-RATE ON CONTAMINANT EQUILIBRIUM-TIMES AND LEVELS IN SEALED CABINS WITHOUT AIR PURIFICATIN EQUIPMENT, ASSUMING CONSTANT CONTAMINANT GENERATION RATE
Effective Gaseous Volume of Cabin: 8.49 m3 (300 ft3)
Total Pressure: 253 mm Hg (5 psia)
Temperature: 26°C (78.8°F)
Atmosphere: Single gas, O2
Contaminant Generation Rate: 0.1 ppm/day (0.26 mg/m3/day)
Average Molecular Weight: 64
Leak Rate expressed in lbs/day O2
Equilibrates at 21.2 mg/m3 in approx 250 days
0.1#/day
0.5#/day
0.1#/day
0.5#/day
0.75#/day
1.0#/day
1.5#/day
2.0#/day
3.0#/day
5.0#/day
Concentration (mg/m3)
Time (Days)

FIG. 5



CONTAMINANT CONCENTRATION ALONG TIME BED



CONTAMINANT CONCENTRATION IN GAS LEAVING BED

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13. ABSTRACT

Atmospheric contaminants in sealed cabins originate from a multitude of sources: off-gassing from cabin materials, production of contaminants by the life support system components, and the end products of human metabolism. The scope of the problem increases with progressing mission duration and can become the limiting factor for man's tolerance to extended space flight. Several important aspects must be considered: truly uninterrupted, continuous exposure, a combination of physiological stress from the use of artificial atmospheres and the chemical stress imposed by the trace contaminants, and the great potential of synergistic toxic effect by various constituents of the highly complex misture of many contaminants. Superimposed on these factors are the other aggravating characteristics of prolonged space flight: logistics problems of life support and psychological effects of isolation on performance. Clearly, these factors must be weighed singly and in combination to allow safe design of future manned systems. Validation of human tolerance to trace contaminants can be accomplished by prolonged animal exposures coupled with mathematical model verification. Tradeoffs in life support system design can extend tolerance to contaminants and long range logistic tradeoffs should be considered by utilizing extraterrestrial resources for contaminant removal purposes.

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