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**A MODEL FOR PREDICTING CENTRAL NERVOUS SYSTEM TOXICITY
FROM HYPERBARIC OXYGEN EXPOSURE IN MAN:
EFFECTS OF IMMERSION, EXERCISE, AND OLD AND NEW DATA**

A. L. Harabin
S. S. Survanshi
L. D. Homer

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Naval Medical Research
and Development Command
Bethesda, Maryland 20889-5606

Department of the Navy
Naval Medical Command
Washington, DC 20372-5210

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TECHNICAL REVIEW AND APPROVAL

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The experiments reported herein were conducted according to the principles set forth in the current edition of the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This technical report has been reviewed by the NMRI scientific and public affairs staff and is approved for publication. It is releasable to the National Technical Information Service where it will be available to the general public, including foreign nations.

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13. ABSTRACT (Maximum 200 words) We analyzed symptoms of central nervous system (CNS) oxygen toxicity from 1726 controlled human hyperbaric O ₂ exposures at PO ₂ (partial pressure of O ₂) levels ranging from 0.3 to 2.9 atmospheres (atm) using risk models and maximum likelihood analysis, and tested specific hypotheses with likelihood ratios. The data were sorted into dry and immersed, no-exercise, and exercise conditions; new studies were separated from those before 1972. The analysis showed that CNS toxicity, in contrast to pulmonary, increases non-linearly with O ₂ level (power on O ₂ > 2) and time: the longer an exposure has been, the riskier additional exposure becomes (power on time > 1.2). Immersion and exercise each significantly increased the risk of toxicity at any PO ₂ and time combination. Older studies of immersed, exercised subjects predicted significantly more risk than new studies conducted under comparable conditions and could not be combined for parameter estimation. Reasons for this incompatibility are discussed. Parameters obtained from only the new data predict that current U.S. Navy depth/time limits for O ₂ diving should keep the incidence of O ₂ toxicity below 1%, provided recommended purging procedures are followed.				
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INTRODUCTION

Exposure to 100% oxygen (O_2) under hyperbaric conditions can produce symptoms of central nervous system (CNS) toxicity. These symptoms include nausea, paresthesia, tinnitus, twitching, tunnel vision, unconsciousness, and convulsions (1). Despite these hazards, pure O_2 is used by Navy divers. The apparatus they employ recirculates and removes CO_2 from the breathing gas and thus permits swimming without production of bubbles on expiration. In order to avoid drowning due to convulsion or other debilitating symptoms of CNS toxicity, there are mandatory limits on the time of exposure for O_2 breathing (2). At deeper depths, these time limits are shorter than at shallow depths. These depth-time limits were extended recently (2) as a result of an informal analysis of new experimental data (3).

In this report, we fit models to human data in order to make predictions of the development of CNS toxicity as a function of exposure condition. High PO_2 's (partial pressure of oxygen), prolonged exposures, and exercise appear to hasten the onset of toxicity. The shape and relationship between PO_2 and human CNS toxicity has not been determined. Is it linear as suggested by models of human pulmonary toxicity (4), or more steeply dependent on PO_2 , as in the development of toxicity from hyperbaric O_2 exposure in guinea pigs (5)? The distinction is important for the design of safe PO_2 limits for human exposures. It is also important to know whether toxicity increases linearly or more rapidly with time. A good model will permit quantitative assessment of safety of occupational exposures for working divers.

To obtain answers to these questions, we collected results of as many controlled human hyperbaric O_2 exposures as possible. A large series of experiments was recently conducted

by the U.S. Navy in the 1980's. In addition, we analyzed large studies conducted in the United States and in Great Britain in the 1940's. We also collected and included other smaller studies.

We analyzed these data with risk models also known as hazard functions (6), allowing the continuous assessment of risk as a function of PO_2 and time of exposure. We used maximum likelihood to estimate parameters of the models, and computed likelihood ratios to determine which provided the best fit (6).

METHODS

Data

We found 13 separate studies with a total of 2,170 exposures of human subjects exposed to 100% O_2 . Of these, 688 exposures are modern studies, recently completed under conditions experienced by a working diver. Original records were usually obtained to supplement and verify published summaries. In most cases, communication was made with the investigators. Only minor discrepancies between published summaries and records were found, and in these cases, the data from the original records were used. The complete data are available in a report (18). The data for the model consisted of the depth and duration of the O_2 exposure, whether or not a symptom terminated the exposure, the time that the symptom occurred, and whether the subjects were dry or immersed, exercised or not exercised.

Although all data were obtained with subjects breathing 100% O_2 , careful inspection of reports and original records revealed that uniform attention was not given to achieving and

maintaining 100% O₂ in the inspire. In dry studies, leaks of air into and around mouthpieces and masks have been shown to result in an inspired O₂ fraction (FIO₂) of 0.9 (1). In studies using breathing rigs where gas was recirculated and CO₂ absorbed, PO₂ was very dependent on the number of washouts of the lung and breathing circuit that were made (19), because of washout of nitrogen (N₂) from the lung and other body stores. In 1949, Schaefer measured PO₂ with the recirculating apparatus of that era and found FIO₂ to be around 0.8 (12) with one flush. This is consistent with the recent study (19), which showed that FIO₂ obtained from a single fill-and-empty procedure using the current design of rebreathing apparatus is 0.74 and that 3 or more are required to approach an FIO₂ of 1.0. Young (20) found FIO₂ to be approximately 0.8 with some of his deeper exposures. New studies (3,7-10) mentioned frequent and careful washout of lung N₂ along with measurement of certain old studies also described careful attention to lung washout (1,14). We used the best estimate of FIO₂ in the analysis as indicated in Table 1.

Symptoms of O₂ toxicity are listed in Table 2. We made no distinctions among these symptoms as they all were serious enough to the investigators to halt the exposure. (However, an additional analysis using only symptoms 6 through 10 gave similar results which will be discussed). In our analyses we did not include symptoms reported as probable but not serious enough to halt the exposure (27). One study on dry-exercised subjects had many instances where long exposures at high PO₂'s evoked responses of toxicity less often than exposures of lower severity (20). We omitted these data from our analysis along with a small data set representing the only other study on dry-exercised subjects (21). This left us with 11 studies with a total of 1726 human exposures giving rise to 645 instances of toxicity, exposure times

as long as 268 min, and PO₂'s from 0.3 to 2.9 atmospheres (atm) (1 atm = 101.3 kPa) summarized in Table 1.

Analysis

We used standard survival analysis definitions and techniques (6) to analyze the relationship between exposure PO₂ and time, and probability of CNS toxicity. The model of instantaneous risk or hazard function (r(t)) we used was based on the expectation that exposure PO₂ and the passage of time would increase the probability of O₂ toxicity.

$$r(t) = a \cdot \underline{pwrt} \cdot (PO_2 - \underline{thr})^{\underline{pwrt}} \cdot t^{\underline{pwrt}-1} \quad (1)$$

The variables PO₂ and t are the exposure PO₂ in atm and time in minutes. The parameter a scales the risk; thr is a threshold parameter in atm abs (atm + 1): if the exposure PO₂ < thr, no risk accumulates, (r(t)=0); pwrt and pwrt are exponents on PO₂ and time respectively that allow for non-linear changes in risk. The case where pwrt = 0 and pwrt = 1 is analogous to radioactive decay in which r(t) is constant over time. We expected that risk would increase with increasing PO₂ (pwrt > 0), and perhaps would do so in a greater than linear fashion (pwrt > 1). We also suspected that pwrt > 1, that is, the longer the exposure has already been, the more quickly additional risk accumulates.

The probability of developing a symptom up to time t is

$$P(t)_{\text{symp}} = 1 - e^{-R(t)} \quad (2)$$

where R(t) is the integral of the instantaneous risk, r(t).

The parameters a , pwrt , pwr , and thr are estimated using maximum likelihood (6) to obtain those that provide the best description of the observations. If an individual exposure (i^{th} trial) was uneventful to the end of the trial at time T_i , the likelihood of this safe outcome is calculated $l_i = \log (1 - P_{\text{symp}}(T_i))$. If a symptom occurred during an individual trial (between the small time interval t_i and $t_i + dt_i$) the likelihood of a symptom occurring at that time is calculated $l_i = \log (P_{\text{symp}}(t_i + dt_i) - P_{\text{symp}}(t_i))$, then the parameters are adjusted so as to maximize the sum of the l_i for all the observations (6,22). We calculated likelihood ratios to determine whether additional parameters statistically improved the fit. The likelihood ratio is calculated as -2 times the difference of log of the likelihoods of free and fixed parameter fits. This ratio is assumed to be distributed as a Chi-square (χ^2) variable with degrees of freedom (df) equal to the difference in the number of parameters being estimated (6). Standard deviation of parameters were calculated using standard techniques (22,23).

RESULTS

Table 1 summarizes the data used in our analysis. These have been arranged according to whether the subjects were exercised or were not exercised and whether the exposure was a dry exposure or whether the subjects were immersed in water. These factors have long been regarded as important in modifying the physiological responses to O_2 (1). As the data were collected, we noted that there appeared to be a much lower incidence of symptoms in the newest studies; therefore, we also sorted the data into old studies (before 1972) and new studies. The column labeled "Times" gives the longest and shortest times for which exposures were conducted.

We examined the reported symptoms to determine if some studies reported minor symptoms with high frequency, while others might be reporting only more serious ones such as twitching and convulsions. Most symptoms were reported in all studies with patterns that did not suggest any obvious bias for or against reporting any particular symptoms. Table 2 summarizes the number of times that each symptom stopped an exposure.

We began by combining all of the data together regardless of exposure condition and fitted them with only 4 parameters (one thr, a, pwrt, and pwrp). Table 3 shows the estimates and standard deviations of the parameters, when each of the four groups is used to estimate its own set of parameters. The fit significantly improved ($p \ll 0.0001$) when we allowed each of the exposure groups to have its own set of 4 parameters. This allows for testing the effect of exposure condition on all 4 parameters. Estimates of pwrt and pwrp are both greater than 1 for all data types; fixing pwrt or pwrp to 1 significantly worsened the fit ($p \ll 0.00001$).

Figure 1 shows data from the studies with immersed, not-exercised subjects exposed to 2.6 atm O₂ (1) and predictions of the fitted model. The cumulative fraction of subjects developing symptoms is plotted against exposure time. The dashed line shows the predictions of the model when pwrt and pwrp were constrained to 1.0 and the solid line is the model prediction where all 4 parameters were estimated freely. The constrained model clearly does not fit as well. Figures 2 and 3 show data along with model predictions and 95% confidence regions. Figure 2 includes data from the old studies of immersed, exercised subjects, and Fig. 3 shows data from the new studies of immersed, exercised subjects. Notice the different scales of both axes in Figs. 1 and 2 compared to Fig. 3. The older studies had exposure-

stopping symptoms develop in far more subjects at much earlier exposure times. The summary of Table 1 and comparison of Figs. 2 and 3 thus strongly suggest that the new studies with immersed, exercised subjects encountered less toxicity than the older ones.

Next we determined how many of the 16 parameters of Table 3 were required to provide a satisfactory fit. By pooling parameters between data when the parameters were close or the standard deviations appeared large, we attempted to find common parameters among data sets. We also wished to find particular parameters that might have distinguished immersed vs. dry, exercise vs. non-exercised, etc.

Very little simplification was permitted without worsening the fit. Only one parameter, pwrt, permitted estimation of a common value for all 4 groups (pwrt = 2.4 ± 0.23) with no significant worsening of fit ($p > 0.3$). Any other simplifications significantly worsened the fit.

This analysis shows that each exposure condition resulted in significantly different predicted risk. The effects of exposure condition are complicated, affecting thr, pwrt, and a. Figure 4 illustrates the differences in predicted toxicity of each of the 4 groups using the appropriate parameters from Table 3.

DISCUSSION

Both time and PO_2 increased the risk of human CNS O_2 toxicity with a power dependence; immersion and exercise significantly increased risk. Old studies of subjects immersed in water and exercised predicted significantly more risk than new studies conducted under the same conditions, prohibiting pooling of these results.

Why was risk greater in older studies?

Several factors could result in newer studies predicting less risk for any PO_2 and time combination than old: differences in frequency and/or nature of symptoms; differences in exposure condition, including FIO_2 , temperature, CO_2 accumulation; or other differences in experimental design features.

In old and new studies, subjects were military personnel. In the new studies professional divers were used exclusively, while in the old studies some of the military personnel were not professional divers. Some of the older studies were continued until a symptom developed, while the newer studies were conducted for preset times chosen to be only slightly longer than those that had been used as limits for U.S. Navy diving applications. There was a greater incidence of symptoms in the old compared to the new studies. To probe whether these design differences (new studies were terminated before symptom development much more often than old studies) could have resulted in biased parameter estimation, we simulated a data set using the parameters from Table 3, line b in which the exposure PO_2 levels were chosen to match the old studies, but with the exposure times cut in half. Even with these shorter exposure times, the simulated data permitted accurate recovery of the parameters. Thus, simulating censoring more like that of the new results did not affect parameter estimation.

The nature and frequency of symptoms reported in new and old studies were similar, as discussed in the Results. In the old studies, Donald (1) was very clear that subjects were to stop the exposure when any symptom "justified its termination", and although Yarbrough's (15) report is less clear, the records indicate that exposures continued if symptoms judged to

be minor developed. In the new studies, investigators were very cautious and specific in identifying signs and symptoms of O₂ toxicity to protect their human subjects. Even in these studies, there were occasions where minor symptoms were not reported until after completion of an exposure. We did not count these as toxicity episodes because they did not stop exposures. All studies thus seemed to have had the same goal as we do in developing this model: that of utilizing mission-disabling symptoms. Furthermore, we suspect that differences in approach should have led to less frequent or later recording of toxicity for any given O₂ dose in the 1940's than in the 1980's, but Fig. 4 shows that the opposite occurred.

As a final test of the role of symptom choice, we analyzed old and new data considering only symptoms 6 through 10 as positive outcomes, as these might be viewed as less subjective and perhaps more serious. We also tried assigning a weight of 0.5 to symptoms 1 to 5. Using both approaches, we recovered parameters that were within the confidence regions of those obtained when we used all symptoms in the analysis.

Other differences in exposure conditions, including FIO₂, temperature, and FICO₂ do not appear to distinguish the studies from these two eras. In all of the new studies and one of the older studies (1) (and personal communication with K. Donald) great care was taken to maintain FIO₂ near 1.0. Of course, the modern studies benefit from vastly improved technology for gas measurement. Regarding temperature effects, Donald (1) showed that water temperatures at 49° or 88 °F exacerbated symptom development compared to 65 °F exposure, but both old and new studies were performed in 65-70 °F water. With rebreathing circuits, CO₂ accumulation is possible and this could shorten the time before symptom development by vasodilating the cerebral circulation. High levels of CO₂ certainly exacerbate

CNS toxicity in animals (24). There is no strong evidence to support the idea that CO₂ accumulation was systematically greater in the older studies. Donald's subjects carried out frequent purges to maintain a high FIO₂; he also reported discrete measurements of inspired CO₂ of 0.1 to 0.2% (1).

The remaining source of difference between the old and new studies is the type of exercise. Although it appears that work intensities were not different, the new studies all used an underwater bicycle (leg) ergometer, while the older studies employed continuous arm exercise in the upright position. Arm exercise produces a greater increase in heart rate for any oxygen consumption than does leg exercise and results in greater heat loss (25). With greater heat loss at similar oxygen consumptions, the older studies may have had slightly lower brain temperatures with higher attendant convulsion risk. Additional experiments will be necessary to test the hypothesis that arm exercise exacerbated toxicity.

Increased risk due to immersion and exercise

Immersing a subject increases the probability of CNS O₂ toxicity for any PO₂ and time combination; exercise also increases the risk of CNS O₂ toxicity (Fig. 4). The conclusion about immersion is reached by contrasting older data sets of non-exercising subjects, some of whom were dry and some immersed. In these sets, a number of the investigators were involved in both kinds of studies. The conclusion about exercise is reached from old studies of immersed subjects: some exercised and some not. In this case also, some of the investigators contributed to both kinds of studies. This reduces the chance that either conclusion might be based on variability in the conduct of the studies rather than on the conditions of exposure.

Despite the fact the exercise effects were demonstrated long ago by Donald (1), the mechanisms are not understood. Lambertsen and coworkers (25) showed that the response to exercise is different when a subject breathes hyperbaric O₂. Arterial PCO₂ remained the same or decreased slightly when subjects exercised on the surface. In the same subjects, exercising while breathing O₂ resulted in a higher PaCO₂. Cerebral blood flow could be augmented, resulting in an increased tissue O₂ tension and the delivery or presence of deleterious substances (e.g., free radicals) responsible for toxicity. Similarly, immersion could increase cerebral blood volume. Exercise may have elevated brain temperatures very slightly, which could accelerate the processes that show non-linear dependence on time and PO₂. These remain interesting research questions.

Prediction of risk for occupational exposures

Because the old and new studies of immersed, exercised subjects could not be pooled and we found no satisfactory explanation for the differences, it seems prudent to use only the parameters estimated from modern results for discussion and predictions of risk of occupational exposures. Figure 5 shows the model predictions using only the new data for depth and time combinations that were tested.

The U.S. Navy Diving Manual (2) specifies fixed exposure times as a function of depth (PO₂) for Navy applications, and these limits are shown in Table 4. These single- depth O₂ limits were recently extended to these values based on an informal analysis of some of the new data analyzed here (3). In Fig. 6 we used parameters obtained only from the new studies of immersed, exercised subjects (Table 3, Line A) to show the predicted risk and 95% confidence regions for these time/PO₂ combinations. Our model suggests that these new

exposure limits may not be of equal risk. The long shallow limits may have a higher probability than the deeper ones: 240 min is permitted at 25 feet of seawater (fsw) (0.75 atm), and our model shows about a 8% probability of some symptom developing in this time, while 10 min at 50 fsw (1.52 atm) carries only a 2% probability.

As mentioned, these exposure limits were based on an informal analysis of most of the new studies of immersed, exercised subjects (3). In this analysis, Butler and Thalmann (3) concluded that a convulsion observed at 0.8 atm was experienced by a diver of unusual sensitivity and that 5 other exposure-stopping symptoms (3 at 0.6 atm, 1 at 1.1 atm, 1 at 1.2 atm) were not O₂-related. If we excluded either of these subsets of symptoms from our analysis, there was little effect on the predicted risk of the depth-time limits shown in Figs. 5 and 6. However, excluding both of these subsets of symptoms results in a model that predicts negligible risk at 0.8 atm and below. We preferred to include all exposure-stopping symptoms (as all were typical of CNS O₂ toxicity) and to accept the observed convulsion at 0.8 atm as sampling the underlying distribution of sensitivities.

Another important factor in evaluating the risk of CNS toxicity of these new Navy O₂ exposure limits (Table 4 and Fig. 6) is the actual FIO₂ to which the diver is exposed. The recommended FIO₂ is not 1.0; the Navy recommends that divers carry out only one fill and empty procedure to wash out lung N₂. Butler and Thalmann (19) have shown that this procedure will produce an FIO₂ of 0.74. If this procedure is followed, the model predicts that the probability drops to <1% at every depth for the times noted in Table 4. The probability of developing CNS O₂ toxicity from breathing nearly pure O₂ at 30 fsw for 80 min is about 4%. If the recommended lung washout procedure is followed to fill the breathing apparatus,

resulting in an FIO_2 of 0.74, the probability of toxicity after 80 min is less than 0.1%. If all current recommendations are followed, Navy limits are safe.

Are there warning symptoms before convulsions?

This analysis permitted us to examine the data available to answer the question whether convulsions are preceded by a more minor symptom (27). In the modern studies (3,9,10), of 8 reported convulsions 2 were preceded by more minor symptoms (dysphoria and nausea), while the other six had no warnings or one immediately before seizure onset. Donald carried out a series in which subjects were monitored through development of "warning" and "end" symptoms (1). Of these 30 exposures, 7 resulted in convulsions or unconsciousness and 5 were preceded by twitching or nausea. The data thus are equivocal: about half of the time, minor symptoms preceded convulsions by 5 minutes or more. In any case, the utility of this model is in the prediction of the likelihood of mission completion. Whether or not other symptoms portend convulsions may not matter if other symptoms interfere with a working diver's performance.

SUMMARY

This analysis of results from human hyperbaric O_2 exposures shows that old and new studies on immersed exercised subjects cannot be pooled for risk predictions. Using only the new studies our analysis shows a strong non-linear dependence of probability of CNS O_2 toxicity on both time and O_2 level. This finding is consistent with our previous study in guinea pigs exposed to hyperbaric O_2 (5). Human CNS toxicity appears to follow different kinetics than those for pulmonary toxicity (4); decreases in vital capacity are linearly

proportional to the time and PO_2 tested. With human hyperbaric O_2 exposure, additional increments of exposure time incur more risk as exposure length increases ($\underline{pwrt} > 1$), and the same amount of time at increasing depths represents more than a linear increase in risk ($\underline{pwrt} > 1$).

As with all models, this one needs to be tested with predictions and new experimental results. Many interesting and important questions remain about O_2 toxicity which might benefit from quantitative analysis. Does inert gas exacerbate symptom development (i.e., how does risk accumulate with multi-level O_2 exposures?)? Are the kinetics of recovery from O_2 toxicity similar to those of the onset of risk? The question of wide variation in individual susceptibility was proposed long ago (8) and invoked recently to explain some results (2). We have assumed here that the pool of subjects in each study represents a sample from a single underlying distribution of susceptibilities. Further examination of this assumption should prove interesting.

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TABLE 1

Summary of data sorted by exposure condition.

<u>Data Set</u>	<u>Source</u>	Exposure PO ₂ (atm)	Times (min)
Immersed, Exercised, New			
19/688			
0/12	Piantadosi, et al., 1979 (7)	0.7	68-268
4/18	Schwartz, 1984 (8)	0.9	37-250
15/658	Butler, 1984 (9), 1986 (3), 1986 (10)	1.5-0.6	5-240
Immersed, Exercised, Old			
135/275			
114/161	Donald, 1945 (1)	1.5-0.8	3-120
14/49	Schaefer, et al., 1949 (11,12)†	0.8, 0.5, 0.3	30-89
7/56	Lanphier, et al., 1954 (13)	1.4-0.5	8-113
0/9	Alexander and Flynn, 1971 (14)	0.3	240
Immersed, Not-Exercised, Old			
368/619			
271/399	Donald, 1945 (1)	2.9-0.8	3-120
97/220	Yarbrough et al., 1947 (15)†	2.2, 1.7, 1.3	7-120
Dry, Not-Exercised, Old			
112/144			
2/9	Behnke et al., 1935 (16)*	2.6, 1.7, 0.8	43-180
17/17	White, 1945 (17)*	2.6	9-39
39/42	Donald, 1945 (1)	2.5, 1.7	6-180
54/76	Yarbrough et al., 1947 (15)*	2.6, 2.1, 1.5	8-129
Total			
645/1726			

N_{sympt} = Number of exposures terminated by a symptom; N_{tot} = total number of exposures; FIO₂ ≥ 0.95 except: *

FIO₂ = 0.9; † FIO₂ = 0.8

TABLE 2Symptoms of CNS O₂ toxicity recorded.

	Number reported
1 nausea	75
2 irritability, dyspnea, sleepiness, dysphoria	12
3 headache	5
4 numbness, tingling	13
5 dizziness, vertigo	63
6 twitch	335
7 hearing disturbance	7
8 visual disturbance	17
9 unconsciousness, aphasia	16
10 convulsion	91
Total	<hr/> 634

TABLE 3

Estimates of parameters and standard deviations (SD).

	<u>pwrt</u>	<u>pwtp</u>	<u>thr</u> (atm)	<u>a</u> x 10 ⁴
A Immersed, Exercised, New	1.7 (0.33)	3.6 (5.1)	0.3 (0.7)	3 (27)
B Immersed, Exercised, Old	1.27 (0.22)	3.0 (1.8)	0.1 (0.4)	47 (47)
C Immersed, Not-Exercised, Old	1.22 (0.21)	2.1 (1.6)	0.7 (0.4)	96 (39)
D Dry, Not-Exercised, Old	1.75 (0.14)	3.0 (1.1)	1.4 (0.3)	18 (18)

TABLE 4United States Navy single-depth O₂ exposure limits (2).

Depth (fsw)	PO ₂ (atm)	Time (min)
25	0.8	240
30	0.9	80
35	1.1	25
40	1.2	15
50	1.5	10

FIGURE LEGENDS

Fig. 1. Comparison of predictions from free and constrained models with observed cumulative fraction of subjects (immersed, not-exercised) developing CNS O₂ toxicity as a function of exposure time. Individual points are the results of exposures to 2.6 (■) atm O₂ in 15 subjects (8) and shown as cumulative fraction of subjects developing symptoms. The continuous line is model prediction of probability of CNS toxicity using parameters shown in Table 3, line C; the dashed line is the model prediction when thr, pwr_t, and pwr_p were constrained to 1.0.

Fig. 2. Comparison of model predictions, confidence regions, and cumulative fraction of observed symptoms of CNS O₂ toxicity as a function of exposure time from old studies of immersed, exercised subjects (8). Solid lines show the model's predictions for 0.8 atm and 1.5 atm using parameters from Table 3, line B. Dashed lines show the 95% confidence regions calculated from propagation of errors (23). Raw data are presented as cumulative fraction of subjects developing a symptom; there were 18 exposures at 0.8 atm (▼) and 46 at 1.5 atm (•) O₂ with about 30 and 70% (respectively) of subjects developing symptoms.

Fig. 3. Comparison of model predictions and observed cumulative fraction of subjects developing symptom of CNS O₂ toxicity as a function of time from new studies of immersed, exercised, subjects. Solid lines show the model's predictions (Table 3, line A) for 0.6 atm and 1.1 atm. Dashed lines show the 95% confidence regions. Data are presented as cumulative fraction of subjects developing a symptom; there were 128 exposures at 0.6 atm (■) and 237 at 1.1 atm (□). Exposures were carried out for fixed times and the observed

incidence was <4% and appeared to be much lower than that observed in the old studies conducted under similar conditions.

Fig. 4. Effect of exposure condition on the probability of developing a symptom of CNS O₂ toxicity at 1.2 atm O₂ . Each line shows the risk calculation from parameters for each of the groups shown in Table 3. 95% confidence regions are not shown, but do not overlap across data sets. Each data set predicted significantly different risk as determined by χ^2 testing.

Fig. 5. Predicted probability of developing an exposure-stopping symptom of CNS O₂ toxicity based on analysis of only the new studies of immersed, exercised subjects.

Parameters shown in Table 3, Line A.

Fig. 6. Probability of developing a symptom of CNS O₂ toxicity under the 1989 U.S. Navy O₂ breathing depth-time limits (2) if an FIO₂ of 0.95 is achieved in the breathing apparatus. These predictions are based on the parameters from new results obtained from immersed, exercised subjects (Table 3, Line A).

FIGURE 1

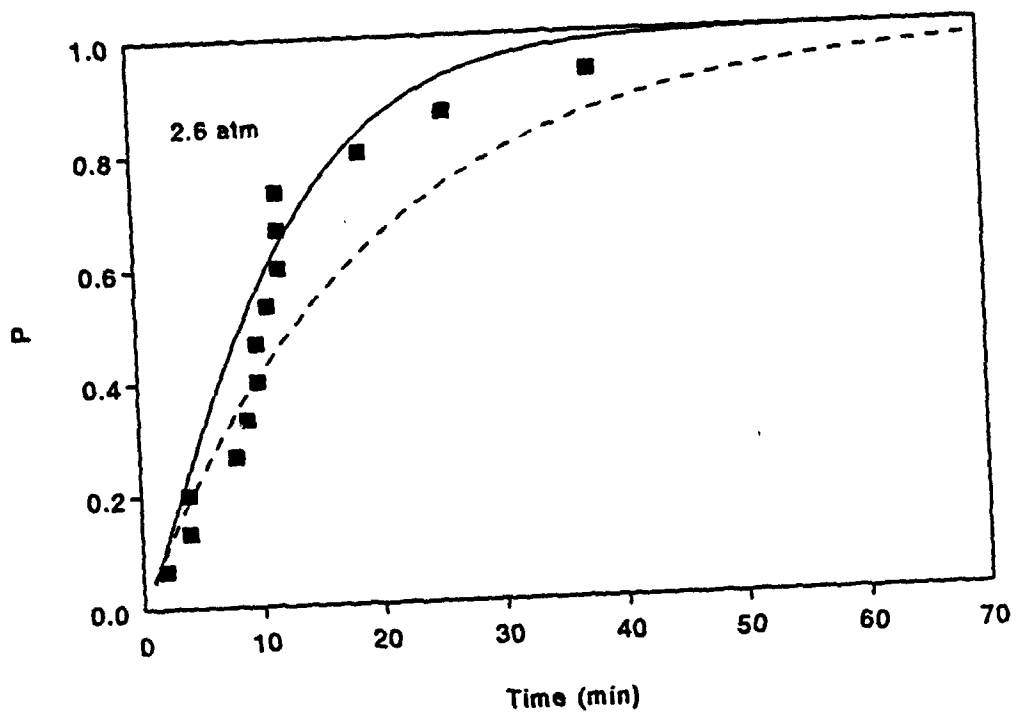


FIGURE 2

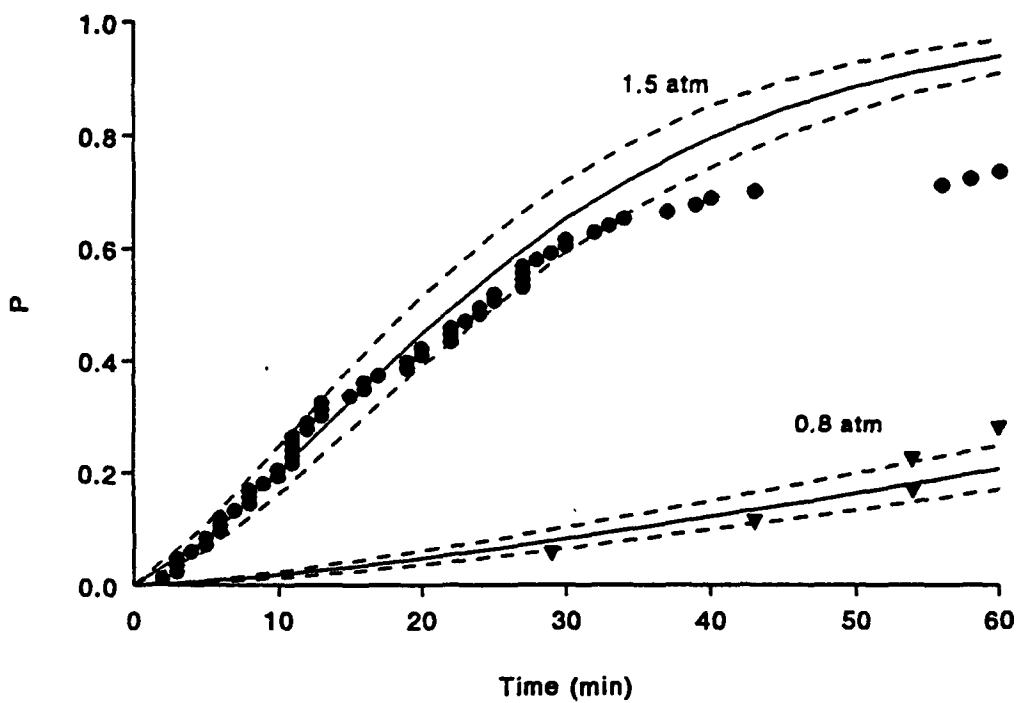


FIGURE 3

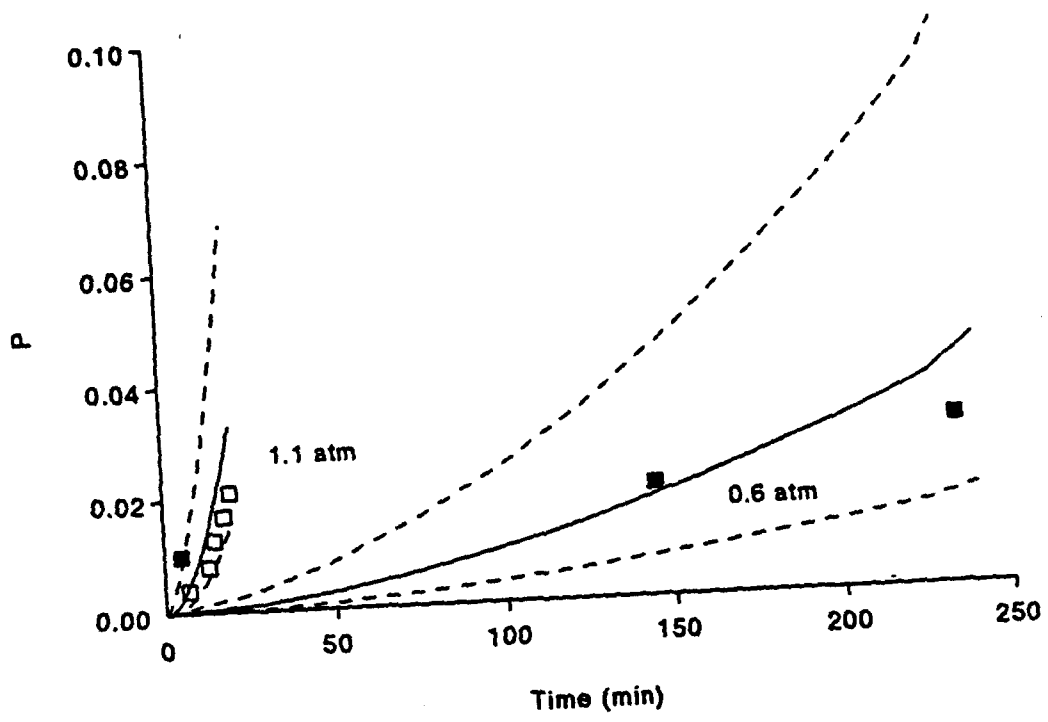


FIGURE 4

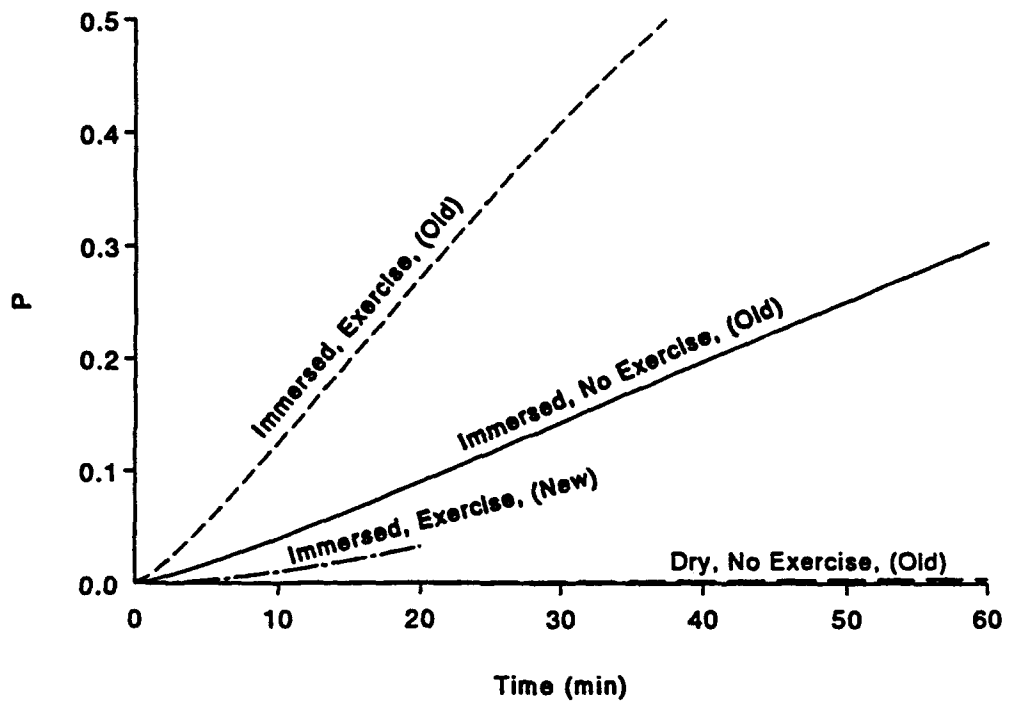


FIGURE 5

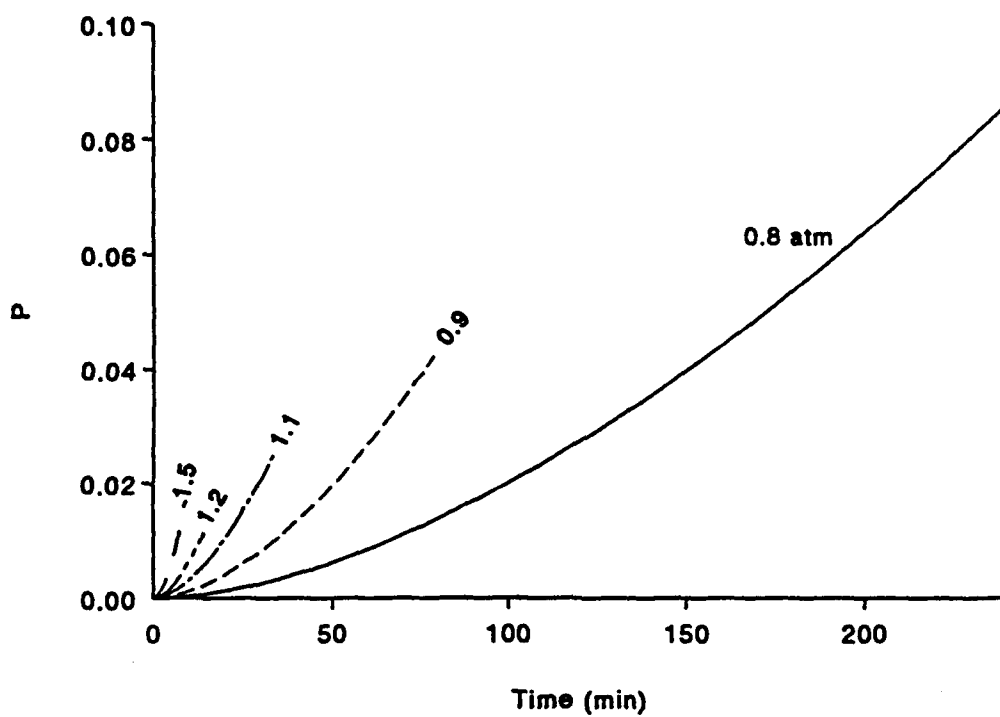


FIGURE 6

