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A STATISTICAL ANALYSIS OF RECENT NAVAL EXPERIMENTAL DIVING UNIT (NEDU) SINGLE-DEPTH HUMAN EXPOSURES TO 100% OXYGEN AT PRESSURE

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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.

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Using the data from 688 human single-depth hyperbaric oxygen (O_2) exposures conducted at the Naval Experimental Diving Unit and reported on from 1979-1986, we developed a mathematical model that can predict the risk of developing symptoms of central nervous system O_2 toxicity as a function of time and depth of exposure. Maximum likelihood analysis with models relating depth and time of exposure to risk accumulation was used to estimate probability of symptom development and confidence intervals. U.S. Navy single depth-time O_2 diving limits were evaluated for safety as a function of actual PO_2 achieved in the breathing apparatus. These results suggest that current limits are not of equal risk. Long shallow exposures might present unacceptably high risk if an FIO_2 = 1.0 were achieved in the breathing rig. Adherence to current recommended purging procedures results in acceptably low (< 1%) risk predictions for all depths.

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INTRODUCTION

Between 1984 and 1986, the Naval Experimental Diving Unit (NEDU) produced an important series of reports dealing with pure oxygen (O_2) diving (1,3,5). Butler and colleagues completed a large series of controlled human exposures, both single- and multi-depth designs, in which immersed, exercising divers breathed 100% O_2 at depths ranging from 20 fsw (1.6 ATA) to 50 fsw (2.5 ATA). In these studies, they carefully monitored the development of symptoms of central nervous system (CNS) O_2 toxicity. On the basis of an informal analysis of this work (5), they recommended extension of the depth-time limits for O_2 breathing as shown in Table 1. These appeared in the 1987 edition of the U.S. Navy Diving Manual (11). The new limits remove the distinction between normal and exceptional exposures and increase permissible exposures.

TABLE 1

Navy limits for O_2 breathing.

OLD		NEW	
Depth (fsw)	Time (min)	Depth (fsw)	Time (min)
10	240		
15	150		
20	110		
25	75	25	240
30	45	30	80
35	25	35	25
40	10	40	15
		50	10

In this report we present the details of a statistical analysis of these human dives and include smaller studies of Schwartz (11) and Piantadosi et al. (10), all conducted at NEDU. All of these dives are the centerpiece of an ongoing analysis of a larger group of human data, but because of the importance of the NEDU studies, extra details are presented here. These results are somewhat difficult to visualize for several reasons. Results consisted of whether or not a symptom developed after a series of hyperbaric O_2 exposures of fixed lengths, most of which were completed safely. In fact, although these studies were designed to test the feasibility of extending U.S. Navy O_2 limits, the exposures were selected with the expectation that they would be safely tolerated. In statistics, "right censoring" is the term used when an experiment is not carried out to completion, that is, until a symptom developed in every subject. Sometimes, however, a symptom of CNS O_2 toxicity developed, and the exposure was terminated. Thus, the results consist of a binomial outcome: either yes a symptom did develop or no a symptom did not develop after an exposure to a given PO_2 and time. Another complication to visualizing these results is the fact that the exposures were not always conducted for the same periods of time. Sometimes technical complications curtailed an experiment. Unexpected results on occasion necessitated changing the length of an exposure. For example, 40 fsw was initially being tested for 20 min (5). After development of several symptoms, the test was shortened to 15 min. Now the data consist of a group of 20-minute exposures with a few symptoms, and a group of safely completed 15-minute exposures.

The statistical techniques probably most familiar to biomedical research require normal distributions and lose discriminatory power when data are right censored. Maximum likelihood (7,9) is another standard statistical method that is perfectly suited to these CNS O_2 toxicity studies.

Data

A total of 688 human O_2 exposures were conducted; about half of these were single-depth, while the other half were multi-depth excursion profiles. In this report we analyze only the single-depth results and have included only the outcome of the time spent at the first depth of the excursion dives. We have also included results of partial dives that had to be aborted for technical reasons. In our analysis, we have assumed instantaneous descent. These studies were conducted with conditions as summarized in Table 2 and more details of specific sources are given in Appendix 1. Subjects were instructed to alert investigators of any symptoms noted and dives were stopped whenever a symptom consistent with CNS O_2 toxicity developed. In some cases, symptoms were only reported post-dive by the subjects. These were categorized as probables in the original reports and in our analysis. Definite symptoms included convulsion, aphasia, twitching and blurred vision, accompanied by tinnitus, dysphasia, and light-headedness.

There were an additional 5 occasions (1 at 40 fsw, 1 at 35 fsw, 3 at 20 fsw and indicated in Appendix 1) when symptoms caused termination of the dive, but were declared probable by the investigators after the dive. These symptoms included tingling,

TABLE 2

Summary of NEDU (1,3,5,10,11) data analyzed.

Depths: 20 fsw to 50 fsw

Times: 240 min to 10 min

Definite Symptoms: blurred vision, twitching, aphasia, convulsion, n = 14

Probable Symptoms: tingling nausea, blurred vision, dizziness, tinnitus, dysphoria, n = 17; 5 of these were dive-stopping and 12 others were only mentioned after completion of the entire dive.

Subjects: U.S. Navy divers and Diving Medical Officers

Breathing Apparatus: Draeger LAR V US Navy Mark I full face mask (except Schwartz (11) who used Emerson and Fenzy units)

FIO_2: >0.95, $FICO_2$: <0.0095

Temperature: 22 °C, (body temperature decreased .25 °C/h)

Exercise: leg ergometer, prone, 6 min work - 4 min rest cycles

nausea, tinnitus, dizziness, light-headedness, retching, paresthesia, and poor concentration. Because these symptoms are all characteristic of CNS O_2 toxicity, we called these 5 occasions dive-stopping probable symptoms and handled these symptoms in two ways. In the first case we included all the dive-stopping probable symptoms along with the definite symptoms and called this category "dive-stopping symptoms." In the second case, we excluded the dive-stopping probable symptoms in accordance with the intuitions of the investigators and called the dive truncated but safe. This categorization

was called "excluding dive-stopping probables." In all there were 31 symptoms; 14 were definite and 17 were probables, 5 of which were dive-stopping.

Model

The goal of a model is to develop an expression that predicts the observed outcome in an experiment. A model consists of an equation or expression that includes factors that are likely to be important in determining the observed outcomes. With CNS O_2 toxicity, important factors are surely time and depth of exposure: symptoms are more likely to develop as more time is spent at any given depth and as the depth of exposure increases, the time that is required to develop toxicity decreases.

In addition to the time and PO_2 dependence of O_2 toxicity, there must be some allowance made for variability in the response. Variability exists in practically all measurements, due in part to the accuracy of the measurements. In biology, variability also arises from a complicated array of often unidentified features that determine the response. Donald (6) has suggested that not only do different individuals have different susceptibilities to CNS toxicity, but that an individual's susceptibility may vary on different days. We thus must also include something about variability in our model for predicting the response to any given PO_2 and time. Because of the above considerations, we have chosen to model symptom development as probabilistic. Rather than declaring fixed depth-time combinations as "safe", we view symptom development as a risk which develops in some fashion with depth and time. Increasing depth or time only makes symptom development more probable, never switching from "safe" to "unsafe". In our model, both variables (depth and time) may take on powers, so that their effects can be

stronger. We also allow for a threshold depth that is defined as the shallowest depth that can ever give rise to O_2 toxicity. The mathematical expression for the instantaneous risk of developing a symptom after a given O_2 exposure is:

$$r(t) = a \cdot pwrt \cdot (P_{O_2} - thr)^{pwrp} \cdot t^{pwrt-1} \qquad (1)$$

The parameter a is a scaling factor to calibrate depth and time to risk, thr is the threshold depth in ATA (shallower than this depth, no symptoms would be expected and r(t) = 0), pwrp and pwrt are exponents to permit non-linearity or extra steepness in the dose-response curve, and the variables PO_2 and t are the depth (in ATA) and time (in minutes) of the exposure, respectively. Larger values of parameters will lead to increased steepness and convexity in the dose response.

The formula for getting from the risk function to the probability of completing a given O_2 dive safely is:

$$P_{safe} = e^{-\int_0^t r(x)dx} \qquad (2)$$

A few trial calculations will show that as PO_2 or time increase, P_{safe} gets smaller. The probability of developing a symptom (P_{symp}) at time t is calculated as the difference between P_{symp} at 2 times separated by a small interval (we used 2 min).

The goal of the modeling is to choose the parameters a, pwrp, pwrt, and thr so that the predicted outcomes match the observed. That is, we should predict a high

probability of symptom development at depths and times when they were actually observed. The probabilistic formulation says that a symptom becomes more and more likely as depth and time increase, but allows for a range of responses - some early and shallow, some late and deep, but the extremes are less "likely". To do this we use a computer program (9) and a standard technique called maximum likelihood. The likelihood (L) is calculated:

$$L = P_{(obs\ 1)} \cdot P_{(obs\ 2)} \cdots P_{(obs\ n)} \qquad (3)$$

where P_{obs} is the probability of each of the actual outcomes (all P_{safe}, P_{symp} from a series) of n observations in an experimental trial. By adjusting the values of a, thr, pwrt, pwrp, the predicted probabilities will attempt to match the observed or to maximize the likelihood. If, for example, 2 out of 10 divers developed a symptom after 20 min at 40 fsw, we want the predicted probability for that dive profile to be 0.2.

We calculated the likelihood ratio, a formal statistical test, to judge whether one model (or set of parameters) is better than another (7).

RESULTS

The parameters (and standard deviation) that gave the maximum likelihood are given in Table 3. Line a shows the best parameters obtained when all symptoms (both definite and probable) were considered positive outcomes whether or not they stopped the dive. This is the most conservative way of handling the results, but probably of the least interest in design of operational exposure limits. Symptoms that were, in general,

not reported until after completion of the experimental dive, would most likely also not compromise the completion of an actual field exposure. Line b was obtained by including all the dive-stopping symptoms. This analysis included the 5 symptoms that stopped the dives, but were later judged not to be O_2-related by Butler and colleagues. Line c lists parameters obtained using only symptoms that were classified as definite in the original reports.

Progressive exclusion of symptoms from the analysis resulted in parameters that lead to predictions of decreasing risk, which are due to smaller gains, and higher thresholds. Figure 1 shows the predicted probability of developing a symptom of CNS O_2 toxicity as a function of PO_2 and time for parameters obtained when only

TABLE 3

Parameters (±1 SD) for NEDU data.

Symptoms	Ntot	Nsymp	thr	a x 10^4	pwrt	pwrp
a. All (definite + probables)	688	32	1.1 (0.9)	2.7 (14)	1.6 (0.2)	5.2 (6.2)
b. All dive-stopping (definite + dive-stopping probables)	688	19	1.3 (0.7)	2.9 (5.9)	1.7 (0.3)	3.6 (4.8)
c. Excluding dive-stopping probables (definite)	688	14	1.7 (0.1)	1.4 (1.5)	2.4 (0.5)	2.9 (2.6)

dive-stopping symptoms (parameters from Table 3, line b) were considered; Fig. 2 plots risk with the parameters obtained when the 5 dive-stopping probables were excluded (parameters from Table 3, line c) and only the symptoms classified as definite by the NEDU investigations were included. The predictions extend only as long as divers were tested. Excluding the dive-stopping probables slightly decreased the risk for deeper exposures, but nearly eliminated

the risk predicted for 20 fsw dives. This occurred because exclusion of these symptoms resulted in elimination of all 20-fsw symptoms and thus a preference for a higher threshold depth (1.6 vs 1.3 ATA).

DISCUSSION

In this study, we analyzed the NEDU results 3 different ways: (a) including all symptoms (definite and probable in the original reports), (b) including only symptoms that stopped the dives, and (c) including only symptoms that the original investigators judged to be due to O_2 toxicity. The first method is the most conservative and led to the highest risk predictions, but is probably of the least interest in the design of operational limits. Transient symptoms or those that were so minor that they were only reported post-dive would not result in interruption of a working dive. Choosing between the other two was more difficult and did affect the predictions, particularly at 20 fsw. Inclusion of all dive-stopping symptoms (b, rather than relying on *a posteriori* rejection of a few (c) seems preferable for several reasons.

Choice of symptoms included in model

The most serious results of CNS O_2 toxicity and the ones that cannot be tolerated in actual operations are loss of consciousness and convulsion. An important question is whether the less serious symptoms are warnings of convulsions. The actual data available that address this question are summarized in Table 4. In the NEDU studies, there was usually very little warning before development of convulsions. In 2 of the 8 convulsions reported there was a warning of some useful time period (5 min or more), while in the other 6 the warnings were less than 1 min. In some cases the reports even state that efforts were being made to stop the

O_2 exposure, but convulsion intervened.

Also in Table 4 are results from the studies of Donald (6) who looked at first symptom and final symptom in 26 resting subjects exposed to 90 fsw of O_2 in the dry. With 5 convulsions and 2 incidences of unconsciousness, his results are a little different than the NEDU experience. He found that more minor symptoms of toxicity usually did precede convulsion and that the time interval over which the warning was given was long enough to be heeded. Obviously, when humans have been used as experimental subjects, exposures have been halted at the subject's request. Thus it is not really known whether every subject will

TABLE 4

Warning symptoms before convulsions.

Source	Depth (fsw)	Time of convulsion (min)	Time of warning (min)	Warning symptom
NEDU	25	72	immediately prior	apprehension, tinnitus
(1,2,3)	30	82	76	nausea
(wet,	40	20	immediately prior	apprehension
exercising)	40	19	18	tinnitus
	40	2	1	tinnitus
	40	15	5	apprehension
	40	3	immediately prior	breathless
	20	48	47	dizzy, spasms
Donald (6)	90	33	25	twitch
(dry, no	90	32	18	twitch
exercise)	90	30	none	none
	90	27	12	twitch
	90	20	unclear from report	
	90	16 (unconscious)	8	dyspnea
	90	16 (unconscious)	5	nausea

convulse if exposed long enough. Even minor symptoms could have adverse influence on mission accomplishment, i.e., nausea, apprehension, dyspnea, disorientation etc., which could affect decision-making. Thus, it may be prudent to evaluate risk including other

symptoms of CNS O_2 toxicity.

Model validation

Table 5 summarizes the observed outcomes and corresponding predictions of the model using parameters from Table 3, line b (all dive-stopping symptoms used) and illustrates the agreement between the results of the dives and the predictions of the model. In most cases, the predicted % incidence of symptoms lies within the 95% confidence interval of the observed incidence of dive-stopping symptoms. In areas with

TABLE 5

Summary of observations and predictions of NEDU human CNS O_2 toxicity data. Observed incidences and confidence regions are calculated using all dive-stopping symptoms. Model predictions are also derived from inclusion of all dive-stopping symptoms (Table 3, line b).

Depth (fsw)	Time (min)	Ntot Expos	Nprob Symp	Ndef Symp	Ndive Stop Symp	% Obs Incid	95% Conf Int On Obs	Model Predicted % Inciden	Model 95% Conf Int
20	240	35	5	0	2	6	0.7-19	4.7	3-8
	120	93	1	0	1	1	0-6	1.8	1-3
25	240	34	1	0	0	0	0-10	12	7-18
	120	15	0	1*	1*	7	0.2-32	4.6	3-7
	60	14	0	0	0	0	0-23	1.7	1-3
30	90	58	0	5*	5*	9	3-19	6	4-10
35	30	40	1	4	5	12	4-27	2.5	2-4
	25	47	0	0	0	0	0-8	2	1-3
40	20	17	2	2**	2**	12	2-36	2.3	1-4
	15	220	7	2	[illegible]	1	0.1-3	1.5	1-2.5
50	10	58	1	0	0	0	0-6	2.0	1-3
	5	57	0	0	0	0	0-6	8	4-13

*convulsion

many observations, agreement is quite close. In areas with fewer observations (i.e., 40 fsw for 20 min) predicted and observed incidences seem more disparate, but the

confidence region on the observed is so large that it cannot be stated with certainty whether there is disagreement. The area of poorest agreement is at 25 fsw for 240 min. No symptoms were observed in 34 tests, but one serious symptom, a convulsion, was observed after 72 min at 25 fsw (7% incidence). Our model's principle is that risk increases with time, thus the predicted incidence at 240 min must be somewhat higher than that observed at 120 min. Butler and Thalmann (3) believed that this convulsion was experienced by a diver of unusual susceptibility and chose to exclude this as a representative event. Removal of this symptom from our analysis had little effect on our predictions because there were many symptoms at 20 fsw. We prefer to include this symptom and consider the sample of subjects as representative of the underlying distribution of sensitivities. This question of individual sensitivity is important and deserves careful study.

Confidence regions

It is interesting and important to note the magnitude of the confidence bands on observed incidences even when, in human terms, a large number of symptoms was observed. Out of 93 trials of exposures to 120 min at 20 fsw, an incidence of 1% dive-stopping symptoms was observed. This experimentally determined mean represents an estimate of the true underlying mean of the entire population. The confidence one has in having accurately estimated that true mean depends on the number of samples taken. That confidence can be determined by calculation of the 95% confidence interval, which tells you that 95% of the time the true mean will lie somewhere within this range. With a 1% observed incidence in a sample of size 93, the confidence interval includes

incidence rates between 0.03 to 5.8%. This means that if we performed another study of 93 divers, we could expect to observe an incidence anywhere within this range. If the sample size is smaller, the confidence regions get very large, and examples of this can be seen in Table 5 (see for example, 25 fsw for 60 min). Perhaps even more important is the fact that even when no symptoms are observed in an experiment,

TABLE 6

Percent probability of developing symptom of CNS toxicity for U.S. Navy O_2 depth-time limits as a function of actual FIO_2 maintained in the rig calculated from model using parameters noted. 95% Confidence intervals are given below.

DEPTH (fsw)	25	30	35	40	50
TIME (min)	240	80	25	15	10
All Dive-Stopping Symptoms (Table 3, line b))					
FIO_2 = 0.95	8 (4-19)	4 (2-10)	1 (1-3)	1 (1-3)	2 (0.3-11)
FIO_2 = 0.85	0.9 (0.2-5)	0.8 (0.3-2)	0.4 (0.1-2)	0.4 (0.1-1)	1.0 (0.3-2)
FIO_2 = 0.75	«0.1 (0.1-1.3)	«0.1 (0.2-0.7)	«0.1 (0.1-0.4)	«0.1 (0.01-0.4)	0.2 (0.01-0.9)
Excluding Dive-Stopping Probables (Table 3, line c)					
FIO_2 = 0.95	<0.1	2 (0.5-10)	0.9 (0.3-3)	0.9 (0.3-2)	1 (0.2-7)
FIO_2 = 0.85	~0	~0	<0.1	0.1 (0.01-1)	0.4 (0.1-1)
FIO_2 = 0.75	~0	~0	~0	~0	<0.1

depending on the population size, an unacceptably high true incidence cannot be ruled out. For example, 0 out of 57 trials (5 min at 50 fsw) cannot exclude an underlying true

incidence up to 6.7%.

In fact, development and use of a model somewhat improves the confidence of each prediction. By deciding on some underlying relationship (even a simple one such as PO_2 and time each raised to a power, as in our model), all of the data are utilized in a coordinated way. Figure 3 illustrates the confidence bands on the predictions of the model and compares this with some of the individual confidence bands on the experimental groups.

Application

Table 6 summarizes the predicted % probabilities and confidence intervals for the U.S. Navy 1987 single-depth O_2 exposures. Included are predictions based on inclusion or exclusion of the 5 dive-stopping probables. The treatment of dive-stopping probables makes an important difference in predicted risk (given the confidence regions) only on the 20- fsw limit. If the actual percentage of O_2 the diver achieves is near 100%, the risk is not uniform and can be rather high for some of the shallower limits regardless of how dive-stopping probables were handled. In actual operations, the risk will probably not be as high as the FIO_2 = 1.0 entries, because adherence to the recommended filling procedures for the Lar V will result in a lower PO_2. Butler (2,4) analyzed the purging procedures necessary to achieve adequate PO_2 with the Lar V and recommended a single fill technique, which results in an FIO_2 of 0.74. The risk of CNS O_2 toxicity for these depth-time limits drops considerably with FIO_2; and these are also shown in Table 6. It may be important to adhere to the recommended purging procedure, however, so that FIO_2 of 1.0 is not achieved, as this may result in risky conditions at the shallower

depths.

The current study did not specifically evaluate multi-depth exposures, although much of the operational interest will be in excursion diving. In the final report of human O_2 exposures in which excursions from 20 fsw were tested (1), Butler expressed some surprise at the observed outcomes. If, however, the sample sizes and binomial confidence regions on the observations are taken into account, the results were not in conflict with earlier studies. If experience in the field had suggested safety, it is possible that FIO_2 is generally maintained lower than that which was maintained in the laboratory. The incidence of symptoms during the deeper excursions was not outside the confidence regions of the single-depth studies. It would appear that proper control of FIO_2 is important in insuring safety of the current depth-time O_2 limits.

SUMMARY AND CONCLUSIONS

In this report we present a model for predicting the probability of developing a symptom of CNS O_2 toxicity as a function of depth and time of exposure based on results of experimental dives conducted at NEDU. This model permits evaluation of any proposed single-depth O_2 limits (within the ranges studied) and predicts that the current U.S. Navy limits may not be of equal risk. The predicted risk is of concern only if the diver actually achieves an FIO_2 approaching 1.0, which the current purging procedures do not recommend. As with all models, this one awaits confirmation with new experimental results.

REFERENCES

1. Butler, F.K. Central nervous system O_2 toxicity in closed-circuit scuba divers III. Naval Experimental Diving Unit Report No. 5-86, Panama City FL: Naval Experimental Diving Unit, 1986.
2. Butler, F.K. Underwater purging procedures for the Draeger Lar V. Naval Experimental Diving Unit Report No. 6-86, Panama City, FL: Naval Experimental Diving Unit, 1986.
3. Butler, F.K. and Thalmann, E.D. Central nervous system O_2 toxicity in closed-circuit SCUBA divers. In: Proceeding of the VIII Symposium on Underwater Physiology. Bachrach, A.J. and Matzen, M.M. (eds.). Undersea Medical Society, Inc., Rockville, MD, 1984.
4. Butler, F.K. and Thalmann, E.D. Purging procedures with Lar V. Naval Experimental Diving Unit Report 5-84. Panama City, FL: Naval Experimental Diving Unit, 1984.
5. Butler, F.K. and Thalmann, E.D. Central nervous system O_2 toxicity in closed circuit scuba divers II.Undersea Biomedical Research, Vol. 13, pp. 193-223, 1986.
6. Donald, K.W. Oxygen poisoning in man. MD thesis: Cambridge University, 1945.
7. Elandt-Johnson, R.G. and N.L. Johnson. Survival models and Data Analysis. New York: John Wiley & Sons, 1980, pp. 50-75.
8. Harabin, A.L. and Survanshi, S.S. Human central nervous system oxygen toxicity data from 1945-1986. Naval Medical Research Institute Technical Report No. 93-03, Bethesda, MD: Naval Medical Research Institute, 1993.

9. Homer, L.D. and Bailey, R.C. An analogy permitting maximum likelihood estimation by a simple modification of general least squares algorithms. Naval Medical Research Institute Technical Report, Naval Medical Research Institute, Bethesda, MD, 1971.

10. Piantadosi, C.A., Clinton, R.L., Thalmann, E.D. Prolonged oxygen exposures in immersed exercising divers at 25 fsw (1.76 ATA). Undersea Biomedical Research, Vol. 6, pp. 347-356, 1979.

11. Schwartz, H.J.C. Manned testing of two closed circuit oxygen underwater breathing apparatus. U.S. Navy Emerson Rig and Fenzy PO.68. Naval Experimental Diving Unit Report 13-84, Panama City, FL, 1984.

12. U.S. Department of Navy Closed circuit oxygen diving. In: U.S. Navy Diving Manual, Revision 2, Vol. 2, (NAVSEA 0994-LP-001-9020), Washington, DC, Naval Sea Systems Command, 1987.

APPENDIX 1

Summary of individual data sets analyzed.

Piantadosi, 1979 (10): 1 probable symptom/12 exposures

25 fsw	68 - 258 min (154 ± 83)	n = 12	1 probable

Schwartz, 1984 (11): 4 definite symptoms/18 exposures

30 fsw	90 - 220 min (129 ± 77)	n = 18	1 convulsion, 3 definite symptoms

Butler and Thalmann, 1984 (3): 2 definite + 7 probable symptoms/41 exposures

40 fsw	t = 20 min	n = 17	2 convulsions, 2 probables
40	15	24	5 probables

Butler and Thalmann, 1984 (3): 1 definite symptom/29 exposures of first portion

25 fsw	t = 60 min	n = 14	
25	120	15	1 convulsion

Butler and Thalmann, 1986 (5): 5 definite + 3* probable symptoms/304 exposures

25 fsw	t = 240 min	n = 22	0
30	90	37	1 convulsion @ 82
30	82	3	0
35	25	47	
35	30	40	4 definite, 1 probable*
40	15	40	1 probable
50	5	57	0
50	10	58	1 probable

Ibid, 20 fsw: 5 probable symptoms***/108 exposures (first part of excursions)

20 fsw	t = 120 min	n = 73	1 probables*
20	240	35	4 probables**

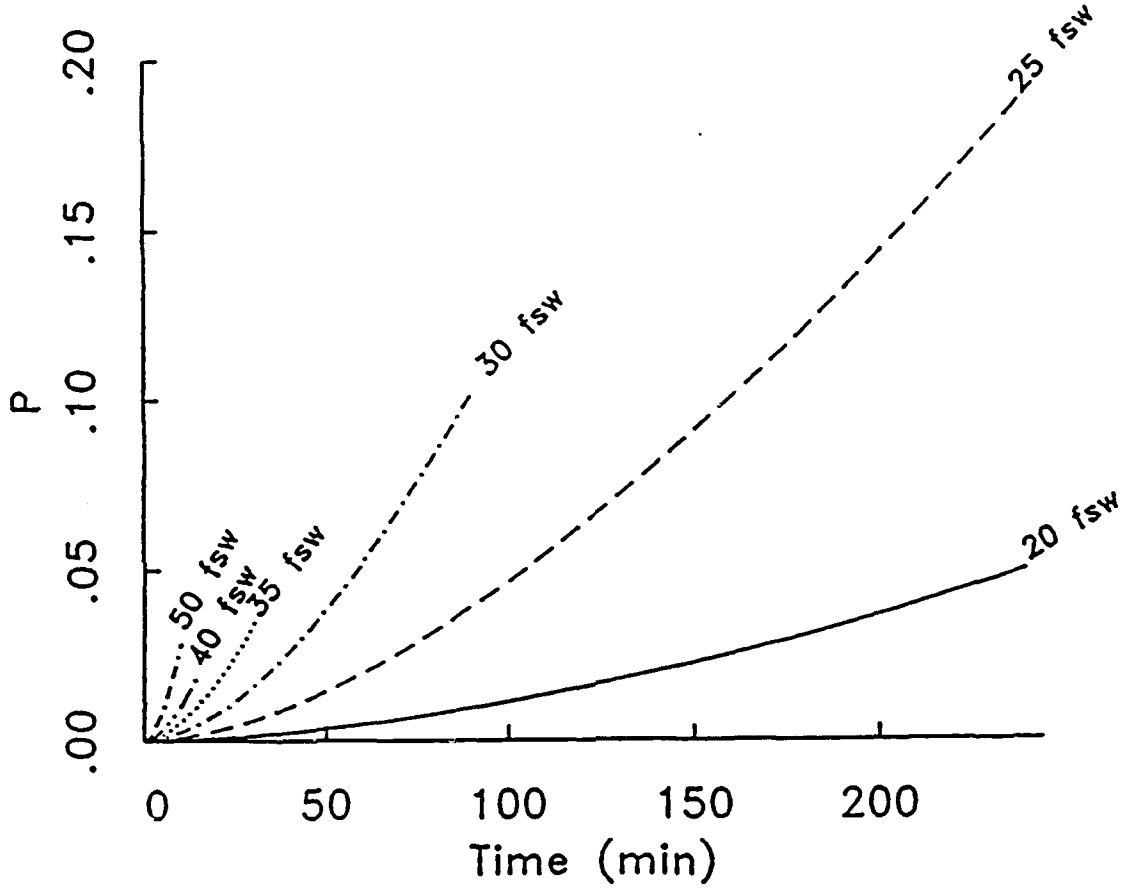
*dive-stopping symptom called probable

Butler, 1986 (1): 2 definite, 1 probable*symptom/176 exposures (first part of excursions)

40 fsw	t = 15 min	n = 92	1 definite
40+,++	15	64	1 definite, 1 probable*
20	120	20	

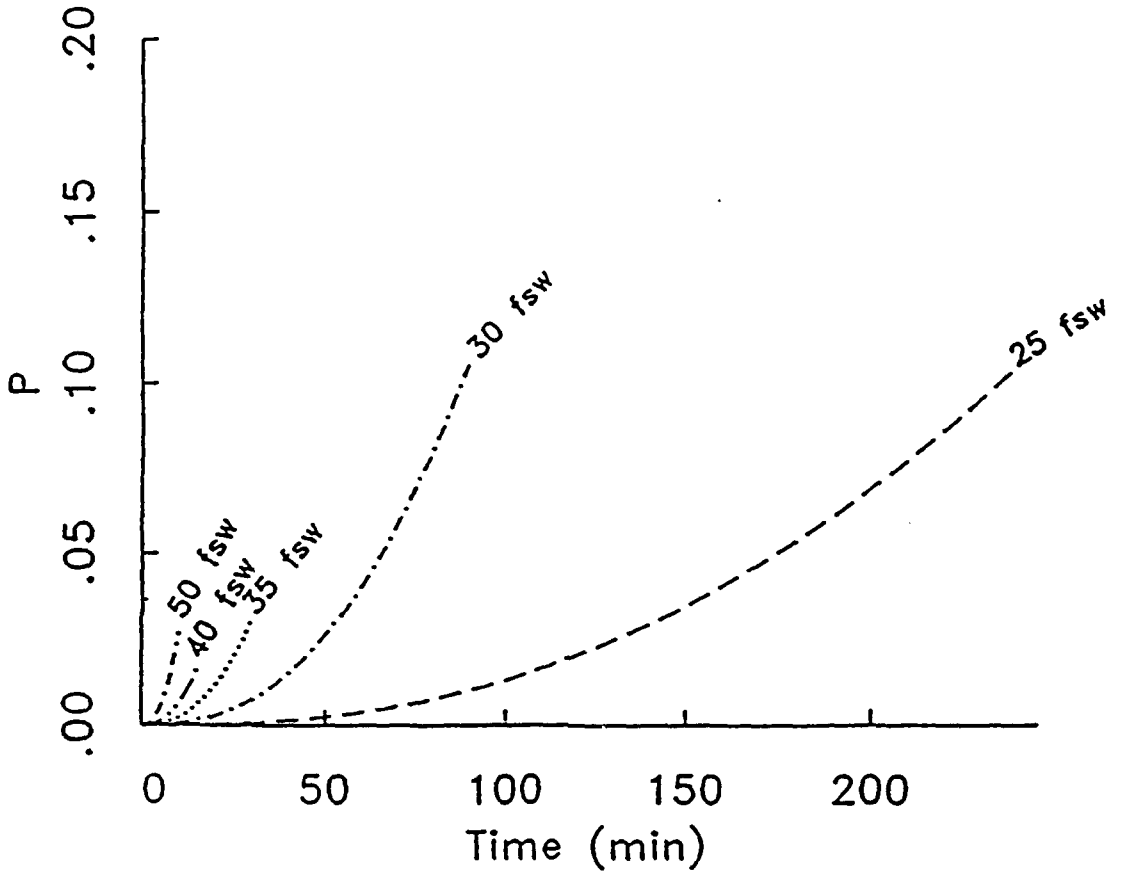
* dive-stopping probable symptom
\+ Reported that "extra sensitive" individuals not used
\++ Some were modified so that FIO_2 = 0.94 and 40 fsw exposure was only 13 min This modification was included in our analysis.

FIGURE 1



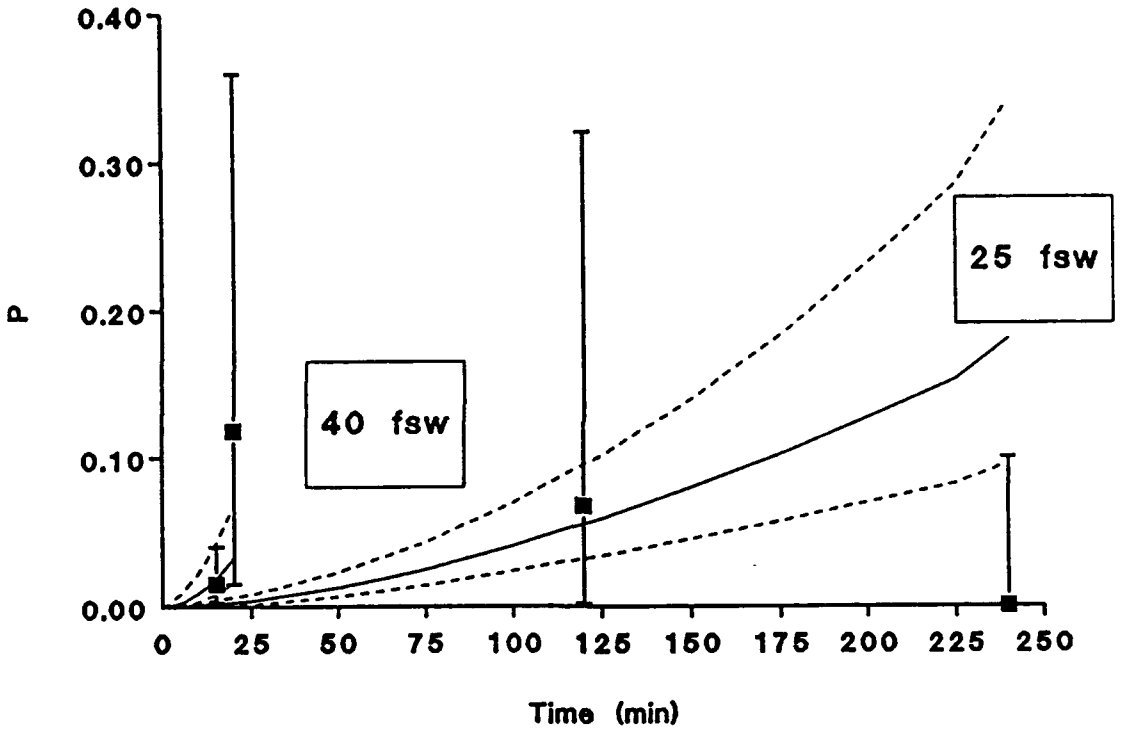
Predicted probability of developing a symptom of CNS O_2 toxicity as a function of depth and time of exposure if the diver maintained an FIO_2 of 1.0 in his rig. Dive-stopping symptoms were used to obtain the parameters listed in Table 3, line b which give rise to these predictions.

FIGURE 2



Predicted probability of developing a symptom of CNS O_2 toxicity as a function of depth and time of exposure if the diver maintained an FIO_2 of 1.0 in his rig. In this case, only symptoms declared definite (dive-stopping symptoms which had been declared probable by NEDU investigators were excluded in the analysis) were included. Parameters listed in Table 3, line c were used to develop these predictions.

FIGURE 3



Data and model predictions. The solid lines show the model's predictions (parameters from Table 3, line b) for 25 fsw and 40 fsw as a function of time. The dotted lines show the 95% confidence region for these model predictions. Individual points are shown with the individual confidence bands for the exposure group.