J Appl Physiol 93: 216–226, 2002.
First published March 8, 2002; 10.1152/japplphysiol.00670.2001.

Using animal data to improve prediction of human decompression risk following air-saturation dives

R. S. LILLO,[1] J. F. HIMM,[2] P. K. WEATHERSBY,[1]
D. J. TEMPLE,[2] K. A. GAULT,[1] AND D. M. DROMSKY[2]
[1]*Biomedical Research Department, Navy Experimental Diving Unit, Panama City, Florida 32407-7015; and* [2]*Environmental Physiology Department, Naval Medical Research Center, Silver Spring, Maryland 20910-7500*

Received 29 June 2001; accepted in final form 5 March 2002

Lillo, R. S., J. F. Himm, P. K. Weathersby, D. J. Temple, K. A. Gault, and D. M. Dromsky. Using animal data to improve prediction of human decompression risk following air-saturation dives. *J Appl Physiol* 93: 216–226, 2002. First published March 8, 2002; 10.1152/japplphysiol.00670.2001.—To plan for any future rescue of personnel in a disabled and pressurized submarine, the US Navy needs a method for predicting risk of decompression sickness under possible scenarios for crew recovery. Such scenarios include direct ascent from compressed air exposures with risks too high for ethical human experiments. Animal data, however, with their extensive range of exposure pressures and incidence of decompression sickness, could improve prediction of high-risk human exposures. Hill equation dose-response models were fit, by using maximum likelihood, to 898 air-saturation, direct-ascent dives from humans, pigs, and rats, both individually and combined. Combining the species allowed estimation of one, more precise Hill equation exponent (steepness parameter), thus increasing the precision associated with human risk predictions. These predictions agreed more closely with the observed data at 2 ATA, compared with a current, more general, US Navy model, although the confidence limits of both models overlapped those of the data. However, the greatest benefit of adding animal data was observed after removal of the highest risk human exposures, requiring the models to extrapolate.

decompression sickness; disabled submarine; hyperbaric; mathematical modeling

PROBABILISTIC MODELS HAVE been used during the last 15 yr to predict decompression sickness (DCS) in humans (22, 23) as well as animals (15). Unfortunately, because of uncertainties about risk factors associated with DCS, such efforts have usually involved empirically fitting functions to dive data, resulting in models that allow risk prediction but lack a sound physiological basis. As a result, these models often do not extrapolate reliably to dive profiles much different from the original data. This can be especially problematic when making predictions about human dives for which there is little or no available human data. These include relevant but high-risk profiles that cannot be performed experimentally because of ethical concerns.

Presently, the US Navy needs the ability to estimate the risk of DCS in a disabled submarine (DISSUB) scenario, which would involve rapid surfacing from air-saturation exposures at pressures up to 5 atmospheres absolute (ATA). Such a scenario would be expected to result in a high incidence of severe DCS. Unfortunately, present decompression models are based on little data directly relevant to this type of exposure and, therefore, should not be expected to produce the most reliable predictions. Previous best estimates of DCS risk for human dive profiles that use mixtures of N_2 and nonelevated O_2 ($<$1 ATA P_{O_2}) have been generated from a decompression model called USN93 (20, 22). However, its intended application was for the depth-time range used in regular Navy diving, not the long, severe exposures of the DISSUB scenario. This model was calibrated with 3,322 human exposures, but only 467 were long enough to be categorized as saturation. Only a subset of these (149 dives) consisted of saturation dives with direct ascent, the type relevant to the DISSUB scenario. As raw data, those human dives demonstrated that direct ascent from ~1.8 ATA would result in perhaps 10% DCS but with nonalarming symptoms, generally slow onset, and good response to standard recompression therapy. However, with the exception of 15 dives at 1.9 ATA, all dives were done between 1.6 and 1.8 ATA. Consequently, human predictions beyond ~1.8 ATA with USN93 should be considered an extrapolation. Nevertheless, this model has been used recently for DISSUB predictions (24), although the model has been shown to substantially underpredict some other types of high-risk human dives (1).

Fortunately, the use of animal data offers the potential to improve prediction of DCS in humans, particularly for high-risk DISSUB profiles. The abundance of high-incidence data, available from a number of animal species and based on a much larger range of pressure, may be more suitable for modeling a range in

Address for reprint requests and other correspondence: R. S. Lillo, Navy Experimental Diving Unit, 321 Bullfinch Rd., Panama City, FL 32407-7015 (E-mail: lillors@nedu.navsea.navy.mil).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

DCS risk compared with human data containing relatively few cases of DCS. Consequently, the dose-response curves for animals are usually steeper than human curves that are derived from low-incidence data (15). However, although a great deal of animal DCS research has been done, there have been only limited attempts to use animal outcome to estimate quantitative human risk of DCS. One reason for this may be the long-standing concern that the much more severe DCS often observed in animals after experimental dives may not be directly relevant to the normally mild cases of joint pain in humans. Although these severe animal cases are often purposely produced by using profiles with inadequate decompression to facilitate the research, differences in symptoms will be an issue with any multispecies approach.

The few attempts to translate from animal to human provide background for the present work. Boycott et al. (4) were among the first to use decompression data from a large-animal model to predict decompression parameters in humans. Through a comparison of respiratory exchange rates in humans and goats, they estimated the saturation time for a goat to be about three-fifths of that of humans. More recently, Berghage et al. (2), building on the work of Flynn and Lambertsen (7), analyzed data from seven species, including humans and rat, from air-saturation exposures with direct ascent. They found that the N_2 "dose" required to produce a 50% incidence of DCS for each species was highly correlated with the average body weight of the species. Lin et al. (17) applied interspecies relationships to calculate decompression schedules for saturation dives at 30 ATA, assuming that saturation half times in four species (human, rat, rabbit, and dog) were related to body weight. They proposed shorter human decompression schedules, although very little animal data were used in their analysis. However, it is not known whether any of these schedules were ever tested on humans. More recently, using maximum-likelihood techniques, Ball et al. (1) fitted linear exponential models to a set of human and sheep air dives (none saturated) with direct ascent. A model that estimated the N_2 kinetics from the combined human and sheep data was found to fit the decompression outcome data better than totally separate human and sheep models. However, this model required species-dependent factors of "gain" (a weighting factor) and "threshold" (the pressure above which the inert-gas pressure begins to contribute to DCS risk).

This report describes the development and evaluation of multispecies (human, pig, rat) models for prediction of DCS after air-saturation dives with direct ascent. The hypothesis being tested is that combining animal data with human data significantly improves the model predictions of human DCS. The differences that we are introducing include differences in models, data, and purpose. We emphasize that this was an ad hoc approach specifically designed to improve the ability to predict risk associated with these types of dives and not to replace other more general models, such as USN93, that are used for a much wider range of profiles. The relatively simple profiles that we are dealing with allowed our use of very simplistic empirical models that are not suitable for more complex situations. By combining three species with differences in severity of DCS, we assume that the decompression responses of these species share a common underlying mechanism(s) that can help to better define the human decompression response. Although these findings may suggest directions for future work, the limited scope of this project prevented the addressing of broader issues, such as general techniques and best types of models for using animal data in this manner.

METHODS

Summary. Hill equation dose-response models were fit, by using the technique of maximum likelihood, to three species (humans, pigs, and rats), individually and in combination. For the main models, a total of 898 air-saturation, direct-ascent dives were used: 245 human dives, 128 pig dives, and 525 rat dives. The predictions of these models were compared *1*) among themselves to judge the benefit of combining species and *2*) to USN93, presently the most used probabilistic decompression model for predicting human outcome, to provide a baseline reference for judging their performance.

Animal use. The experimental protocols for all animal experiments used in this work were reviewed and approved by the Animal Care and Use Committee at the Naval Medical Research Institute [now the Naval Medical Research Center (NMRC)]. The committee used the animal use guidance required at the time of review by the Department of the Navy, which was the current version of the "Guide for the Care and Use of Laboratory Animals" [Institute of Laboratory Animal Resources, National Research Council, DHHS Publication Nos. (NIH) 78-23, 85-23, 86-23].

Intraspecies data used for modeling. All exposures were air-saturation dives, with minimal decompression, from existing published databases and are summarized in Table 1. The models that we developed deliberately did not incorporate gas uptake and washout but assumed saturation before decompression and no important loss of gas during ascent. Saturation was defined as a total bottom time of a minimum of 24 h (1,440 min) for humans, 22 h (1,320 min) for pigs, and 1 h (60 min) for rats. Direct ascent is defined as employing no stops and having a total ascent time after leaving the bottom of $\leq$20 min for humans, $\leq$11 min for pigs, and $\leq$0.2 min for rats.

For humans, a pressure exposure of $>$1 day has been considered saturation. Prior human models actually indicate that 1 day is $\sim$2% short of saturation (20, 22). Twenty minutes was chosen as the maximum ascent time for inclusion in this data set to make the set as large as possible.

Table 1. *Summary of decompression data from the 3 species used for modeling*

Species	Weight	Manifestations	% DCS	Dives, no.
Human		DCS (no marginals)	8.6	245
		DCS (with marginals)	20.8	
Pig	20.0 ± 1.7 kg	DCS (including death)	60.9	128
		Death	33.6	
Rat	245 ± 18 g	DCS (including death)	64.6	525
		Death	46.7	

Weights are means ± SD. DCS, decompression sickness.

Previous modeling suggests that the majority of DCS risk associated with human saturation dives is due to tissues that should off-gas minimally during 20 min of decompression (22).

Because little kinetic information is available for pigs, it was assumed that a bottom time sufficient for human saturation would be more than adequate for saturation in pigs weighing ~20 kg. Pigs were brought to the surface as rapidly as the chamber permitted, which was ≤11 min. In the case of rats, the 1-h saturation requirement is based on prior research (11). A previous study dealing with variable decompression in rats (13) supports the assumption that little gas is lost during the relatively rapid ascent to the surface (≤0.2 min).

Human data. The primary source of human data was the comprehensive NMRC technical report describing the manifestations of DCS after air and N_2-O_2 diving (21). The human data meeting the present selection criteria consisted of 245 dives to depths ranging from 1.61 to 2.00 ATA, with bottom times from 1,440 to 6,181 min. For 65 dives that used an N_2-O_2 mixture containing 0.4 ATA O_2 at depth, equivalent air depths (3) were used to replace the actual depths. Other dives were included that had excursions to other depths, as long as a final 24 h were spent at a constant depth. The 245 dives included *1*) all of the 149 air-saturation dives with direct ascent that were part of the much larger set of dives used to produce the human USN93 model and *2*) an additional 96 human saturation dives. These additional dives included 22 extra dives at 1.91 or 2.00 ATA, representing a substantial increase in higher risk dives over the 15 dives at 1.91 ATA used in the calibration of USN93.

There are a number of cases in which humans complain of minor joint pains and/or fatigue after decompression but in which diagnosis of DCS is unclear. These minor or temporary cases are termed "marginal" in the human data collections. The full cases of human DCS are typically knee pains. Overall DCS incidence for the final 245 human dives used was 8.6% (21 cases) when excluding marginal DCS, and 20.8% when the 30 marginal outcomes were included. Body weights were not available for all of the human dives; therefore, human weight is excluded from the analysis.

To evaluate the feasibility of replacing high-risk human data with animal data, an abridged human data set was created by removing all dives (37 dives) at the two deepest depths (1.91 and 2.00 ATA) and thus with the highest risk, from the original set of 245 human dives. Models were fit to this new human data set both alone and combined with the pig and rat data.

Pig data. The 128 air-saturation pig dives were done at Naval Medical Research Institute/NMRC from 1997 to 2000 and are described in Ref. 5. Dives ranged in depth from 2.52 to 5.55 ATA. Overall DCS incidence was 60.9%; incidence of death was 33.6%. Pig weights before diving ranged from 17.1 to 24.8 kg with a mean of 20.0 ± 1.7 (SD) kg.

Pigs were scored as having DCS if any one of the following occurred: *1*) neurological DCS, *2*) cardiopulmonary DCS, or *3*) death. Neurological DCS was defined as ataxia, paralysis, nystagmus, or repeated inability to stand after being righted twice by the investigator. Cardiopulmonary DCS was defined as a visually observed respiratory rate of >90 breaths/min combined with respiratory distress, as evidenced by open-mouthed, labored breathing, central cyanosis, inversion of the normal inspiratory-to-expiratory ratio, and production of frothy white sputum. These scoring criteria are designed to identify severe DCS, which, in a DISSUB scenario, could result in death or serious long-term morbidity.

Rat data. The 525 air-saturation rat dives were selected from three dive sets analyzed in previous reports (11, 12, 14). Depths ranged from 5.39 to 7.67 ATA with times at depth from 60 to 120 min. For the gas-switching experiments (14), only the control air dives were used. Overall DCS incidence was 64.6%; death incidence was 46.7%. Rat weights after diving ranged from 206 to 316 g, with an overall mean of 245 ± 18 (SD) g.

Rat DCS criteria consisted of walking irregularities, abnormal breathing patterns, forelimb and/or hindlimb paralysis, rolling in the cage, convulsions, and death (12). Animals were scored as having DCS only when one or more of these symptoms developed.

Scoring criteria for modeling. In the main analysis, we chose to exclude human marginal symptoms as less relevant for our main concern. In the animals, we chose to use all occurrences of DCS (which includes death) as the response to the model. Other possibilities are presented in the APPENDIX.

Data analysis: the model. Hill equation dose-response models predicting the probability of DCS were fit to the data of all three species, both individually and combined, by using maximum likelihood (6). Models also evaluated the feasibility of replacing the highest risk portions of human data with animal data. The Hill function is adapted from models previously fit to our rat data (15). These models appear to fit animal decompression well, but we emphasize that they are not based on any known or presumed physiology of DCS.

The dose-response model used for this analysis was the Hill equation

$$\text{Probability (DCS)} = \text{dose}^n/(\text{dose}^n + P_{50}^n) \quad (1)$$

where P_{50} represents the dose at which there is a probability of 50% for the occurrence of DCS, and the exponent n is the order of the Hill equation that controls the steepness of the central portion of the sigmoidal curve. The dose in *Eq. 1* represents a measure of decompression stress and was defined simply as

$$\text{Dose (in ATA)} = \text{depth (in ATA)} - 1 \quad (2)$$

where subtraction of 1 ATA from the depth of the air dive defines the amount of supersaturation existing after ascent to the surface. This definition assumes that *1*) saturation exists before decompression, *2*) all of the additional gas, not just the N_2, is a reasonable prediction metric for DCS, and *3*) no gas loss occurs during the rapid decompression. These assumptions allowed the use of these simplistic dose-response models, as the effect of gas kinetics could be ignored.

Because animal weight may have a significant effect on the decompression outcome within a species, an intraspecies weight correction for dose was included in the model, as previously done for rats, by using a power function (15). Because weights were available for only the animals and not humans, no weight correction was incorporated into the human predictions. For animals, weight (Wt) was first normalized by dividing by the average weight of each species and then raised to an exponent denoted as the weight factor (WtF). The final expression for dose for rats was

$$\text{Dose (Wt corrected)} = \text{dose (Wt/245 g)}^{\text{WtF(Rat)}} \quad (3)$$

and a similar expression was used for pigs by using the average weight of 20.0 kg. By this formalism, the weight factor for humans is fixed at 1.0.

Parameter values of all models were adjusted to maximize the log likelihood of the model with a modified Marquardt nonlinear estimation algorithm (18). The likelihood ratio test was used to evaluate the significance of estimated parame-

Table 2. *Parameter estimates for Hill equation models fit to all 3 species separately or combined*

Species	Separate	Combined
	P_{50}	
Human	1.05 ± 0.06	1.11 ± 0.06
Pig	3.03 ± 0.09	2.97 ± 0.11
Rat	4.74 ± 0.18	4.93 ± 0.10
	Exponent	
Human	7.90 ± 1.75	6.42 ± 0.83
Pig	8.67 ± 2.30	6.42 ± 0.83
Rat	4.67 ± 1.05	6.42 ± 0.83
	Weight factor	
Rat	2.58 ± 0.59	2.00 ± 0.31

Values are means ± SE. Scoring criteria: human DCS (excluding marginal cases) and animal DCS (including animal death). P_{50}, dose (in ATA) at which there is a probability of 50% for occurrence of DCS. Weight factor not significant for pigs and not applicable to humans due to the absence of human weight data.

ters based on improvement in fit (8). The shape of the likelihood surface near the converged parameters was used to estimate the precision of the parameter values. Symmetric confidence limits for predicted functions were generated by using first-order approximation in propagation of error procedures (10).

For each individual species model, parameter estimation produced a single P_{50} and exponent. Weight corrections were then inserted and tested for significance. The species were then combined and fit by an initial model, again containing a single P_{50} and single exponent. The significance of separate P_{50} values and exponents for each species was then tested by introducing additive terms (Δ) for both the P_{50} and exponent

$$P_{50\,human} = P_{50\,rat} + \Delta P_{50\,human} \quad (4)$$

$$P_{50\,pig} = P_{50\,rat} + \Delta P_{50\,pig} \quad (5)$$

$$n_{human} = n_{rat} + \Delta n_{human} \quad (6)$$

$$n_{pig} = n_{rat} + \Delta n_{pig} \quad (7)$$

The approach arbitrarily added adjustment terms to the rat parameters, although these terms could have been added to either of the other two species. By simple inspection of the data, we knew that the positional parameter (P_{50}) would be quite different for the three species but thought that the Hill steepness parameter (n) might be common. Because of the large overall differences in severity between the human and animal DCS, any adjustments in P_{50} or n required for interspecies predictions would reflect differences among species, not only in tolerance to decompression, but also in scoring criteria. The sharing of a common P_{50} or n would be based on partial species overlap of these parameters within the limitations of the data and these relatively simple models. We again emphasize that this approach is based on the assumptions that a common underlying mechanism(s) of DCS exists among species and that the animal dose response may be used to better estimate any common parameters. These are assumed to be true even though signs and symptoms vary with species and dive profile.

Where additive terms were found significant for parameters, the actual value for human and/or pig was estimated rather than found by using *Eqs. 4–7*. As before, weight corrections for the pig and rat were then tested for significance. No adjustment terms for WtF were used, as this parameter was only found significant for the rat (as will be discussed later). Each set of parameters was found by using several dozen sets of starting parameter values to ensure that the maximum log likelihood found was a global and not a local maximum.

RESULTS

Model parameters for single and combined species fits are reported in Table 2 for the main model and Table 3 for the models evaluating replacement of high-risk human data with animal data. Additional analyses examining changes in scoring criteria are presented in the APPENDIX. Only parameters found to be significant at the 0.05 level are presented. As rat weight is shown to have an effect on DCS risk (as discussed below), we emphasize that the plotted curves presented in Figs. 1–6, unless otherwise indicated, are based on a rat weight of 245 g, the average weight of all of the rats.

Single-species models. Models fit separately to the three species showed substantial differences in their P_{50} values, reflecting increasing tolerance (human < pig < rat) to decompression with decreasing species size, as well as differences in scoring criteria. This is graphically shown by the shift to the right, from human to pig to rat, of the predictive curves relating probability of DCS to saturation depth (Fig. 1*A*). In other words, a deeper saturation dive was required to produce the same incidence of DCS in rats compared with pigs, and a deeper dive in pigs than in humans, emphasizing again that the scoring criteria were very different for the three species.

The standard errors for the exponents were up to an order of magnitude larger, on a percentage basis, than those for the P_{50} values (see Table 2). This limited the

Table 3. *Replacing high-risk human data with animal data*

Data	P_{50}	Exponent	Model Prediction, %	
			1.91 ATA	2.00 ATA
Human data	1.05 ± 0.06	7.90 ± 1.75	25(14–35)	41(22–60)
Human data < 1.91 ATA	0.97 ± 0.15	9.86 ± 5.32	34(0–85)	57(0–100)
Human data < 1.91 ATA + animals	1.16 ± 0.10	6.13 ± 0.93	18(7–30)	29(11–47)
Observed			44*(7–52)	38†(18–62)

Human parameter estimates are means ± SE. Human DCS risk predictions (95% confidence limits) are for Hill equation models fit to all the human data, the human data after removal of all dives at the 2 depths ≥1.91 ATA, and the abridged human data set after addition of all the animal data. Scoring criteria: human DCS (excluding marginal cases) and animal DCS (including death). *7 cases in 16 men; †8 cases in 21 men. Values of 95% confidence limits are in parentheses.

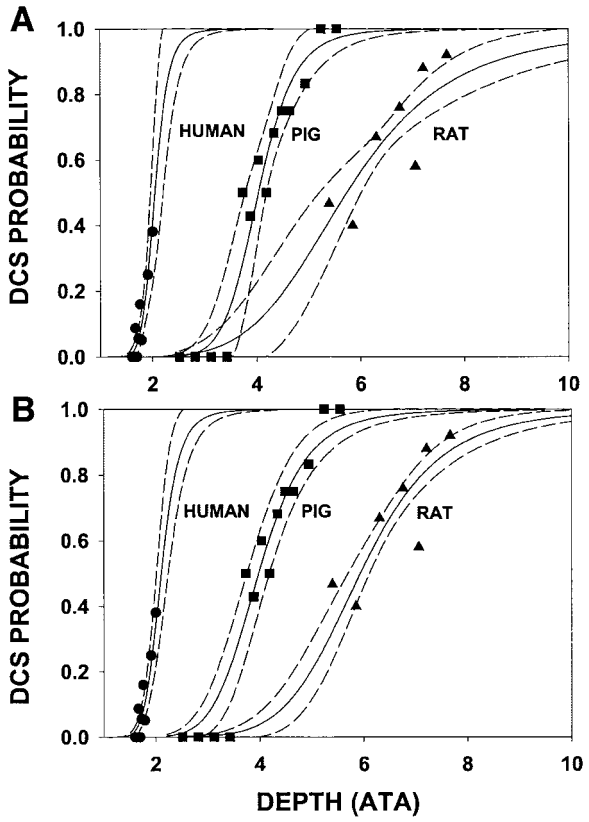

Fig. 1. Predictive curves (solid lines) [and 95% confidence limits (dashed lines)] for single-species (*A*) and multispecies models (*B*) relating decompression risk to saturation depth for direct-ascent air dives are shown for the 3 species. Symbols represent actual data with mean incidence rate of decompression sickness (DCS) calculated for each depth. Rat predictions were based on body weight set at 245 g, the mean weight of all rats.

ability to resolve exponents among species by using their 95% confidence limits. Formal testing of separate vs. combined exponents, described below, also failed to find significant differences among the species. Inclusion of a weight correction (the parameter WtF) produced significant improvement in fit for rats, resulting in a greater probability of DCS for heavier rats after a dive at any depth. However, correction for weight was not found significant in pigs, despite a nearly identical range in weight, in percentage terms, as in the rats, although the much smaller number of pig dives (only 25% of the number of rat dives) would have limited the ability to detect such an effect if it were present.

Similar findings were observed by using alternative scoring criteria, although the specific values for the parameters were different (see APPENDIX).

Multispecies models. Models fit to the combined three species produced separate P_{50} values for each species that were shown to be significant ($P < 0.01$) by applying the likelihood ratio test with the use of *Eqs. 4* and *5*. As expected, these P_{50} values were very similar in magnitude and precision (i.e., standard error) to those from the single-species fits. On the other hand, exponents for the three multispecies models could not be resolved: $P > 0.05$ for both Δn_{human} and Δn_{pig} in *Eqs. 6* and *7*. Admittedly, this finding must be partly attributed to the large estimation error associated with the individual exponents. However, based on these results, a common exponent was estimated for all three species, producing a value with considerably less error than for the single-species estimates. This would be expected, as all the data were now used to estimate one common exponent vs. the previous three, demonstrating one of the major benefits of combining data. However, the value of the common exponent was now a compromise among the three species.

By combining species, the 95% confidence belts around the predictive curves were tightened, compared with the single-species plots (Fig. 1). This was primarily the result of the reduced error associated with the common exponent, which allowed more precise estimates of risk for all three species, particularly in regions in which there were no data. For the human predictions, this benefit was admittedly modest and most evident at the higher incidence levels. Both human and multispecies models agreed well with the observed incidence rate of DCS at 2.00 ATA, the greatest depth for which we have human data (see first 2 models in Table 4). However, combining species also slightly reduced the correlation between the exponent and human P_{50} (-0.84 for human only and -0.68 for combined). This would be expected, as the common exponent was now also influenced by the pig and rat data. The multispecies model had a steeper response (i.e., higher predicted risk of DCS) to increasing depth compared with the USN93 model (Table 4). Thus this Hill model agreed more closely with the observed incidence of DCS at 2.00 ATA, although the confidence limits of both models overlapped those of the data. Very important for future efforts was the inability to resolve any difference between using animal DCS or death for human prediction (APPENDIX). Although differences in diagnosis criteria for animals affected model parameters, our ability to make more precise human predictions was not compromised.

As with the single-species models, a significant ($P < 0.01$) weight correction was found for rats, but not for pigs. Furthermore, the nonsignificant pig weight factor

Table 4. *Model predictions and observed incidence rates for human DCS following air saturation at 3 depths, followed by direct ascent to the surface*

Model	DCS, %		
	2.00 ATA	2.21 ATA	2.52 ATA
Hill human model	41(22–60)	76(51–100)	95(84–100)
Hill multispecies model	34(21–47)	64(46–82)	88(77–100)
USN93 model	17(14–21)	23(19–28)	32(25–38)
Observed			
Current human data set	38*(18–62)	†	†

The 95% confidence limits for both predicted and observed values are in parentheses. Hill model predictions are based on the scoring criteria of human DCS (excluding marginal cases) and animal DCS (including death). USN93 model predictions (22) are based on setting each marginal case of DCS equal to 0.1 of a confirmed case. *8 DCS cases in 21 men; †no data available.

was also shown to be statistically different ($P < 0.01$) from that for rats. An illustration of the large impact that rat weight has on DCS risk is seen in Fig. 2, with the multispecies model. Figure 2*A* shows the dramatic shift to the left of the predictive curves as rat weight is increased in 10-g increments. The net effect is that, for heavier rats, a shallower range of depths is required to produce the same range of DCS incidence. Figure 2*B* plots the predictive probabilities with increasing rat weight at three depths: 5.55, 6.30, and 7.06 ATA. The average slopes for these curves over the 225- to 265-g range were +1.1, +1.2, and +0.9% DCS/g, respectively.

Deletion of highest risk human dives. Results showed that exponent error increased dramatically for the human-only model fit to the abridged human data set (depths <1.91 ATA), producing a much wider confidence belt surrounding the predictive curve, compared with that fit to all of the original human data (Fig. 3, *A* and *B*, Table 3). Consequently, the ability to make meaningful predictions was lost, especially at the greater depths. One disturbing result of the data removal was the failure of the model to resolve risk

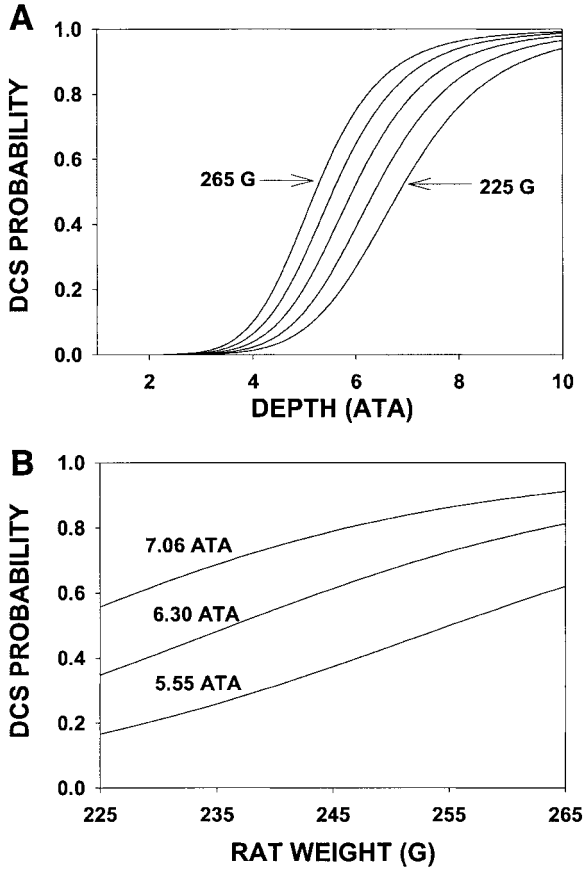

Fig. 2. Effect of rat weight on decompression risk. *A*: dramatic shift to the *left* of the predictive curves as rat weight is increased in 10-g increments, demonstrating that, for heavier rats, a shallower range of depths is required to produce the same range of DCS incidence. *B*: predictive probabilities with increasing rat weight at 3 depths: 5.55, 6.30, and 7.06 ATA. The average slope for each of these curves over the 225- to 265-g range was ≃+1% DCS/g.

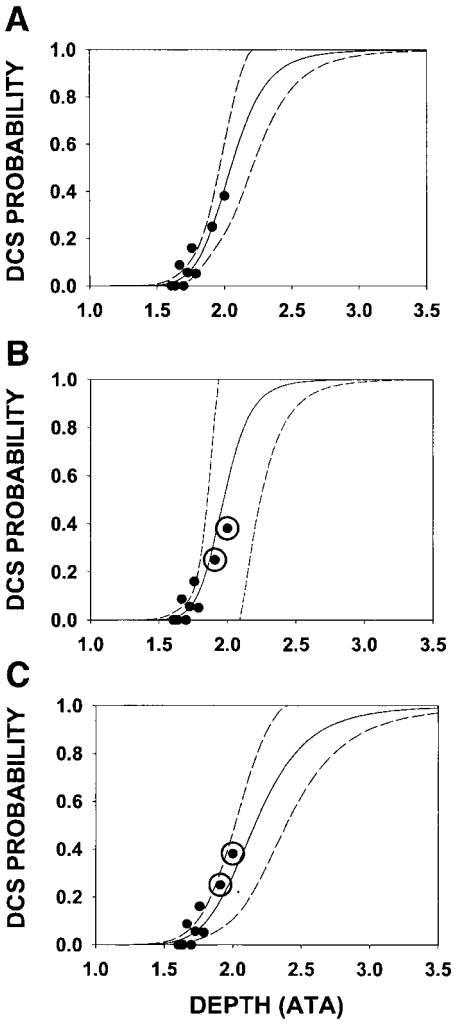

Fig. 3. Replacing high-risk human data (*A*) with animal data. Much of the predictive precision that is lost, after the 37 human dives at the 2 deepest depths ≥1.91 ATA (symbols circled) were removed (*B*), is restored after adding back all of the pig and rat data (*C*). Predictive curves (solid lines) [and 95% confidence limits (dashed lines)] are based on data that exclude human marginals and use animal DCS. Symbols represent human data with mean incidence rate of DCS calculated for each depth.

predictions for 1.91 and 2.00 ATA from zero (Fig. 3*B*, Table 3), although the 95% confidence limits of the actual data at these depths do not overlap zero. This provided little credibility to the poorly defined predictions in this region. However, much of the lost precision was restored to the human predictions after adding the pig and rat dives to the reduced human data set and refitting with multispecies models (Fig. 3*C*, Table 3). This improvement occurred primarily via a reduction in the exponent error. However, the main Hill multispecies model was the best predictor of high-risk human dives in terms of precision. This was expected as this model had the advantage of both the animal data and the most human dives at 1.91–2.00 ATA.

Effectiveness of the models (single species vs. multispecies). The ability of the single species and multispecies models to describe the dive profiles for all three

species was compared by plotting the difference between the model prediction and the observed incidence vs. the saturation depth (Fig. 4). All data were used with the observed DCS values defined as the mean incidence at each depth.

For predictions, rat weight was set at 245 g, the grand mean of all of the rats, as there was no way to set weight in the prediction to truly reflect the weight distribution at each depth. A different symbol was used for each species to allow comparison. In presenting this, we emphasize that actual incidence data have their own associated errors based on the binomial distribution. However, much more important in regard to the rat comparisons is the effect of body weight. As previously discussed by our laboratory (15), the error between the predicted and observed incidence of DCS is magnified in rats by the relatively large effect of body weight on the risk of DCS (~1% increase in DCS per additional gram of rat weight). Consequently, the calculated errors do not truly reflect the performance of the models, as they are based on the mean incidence at each depth, with animals of different weights, and the predictions with the use of the model with a fixed weight. With over a 100-g range in rat weight in the data, this effect obviously can be large. Although these weaknesses will limit interpretation of the residuals, we point out that nearly all of the model predictions are within 25% (absolute) of the observed incidence for DCS for both the single-species and multispecies models (Fig. 4). More importantly, the scatter of points around zero suggests that the models predict DCS for a given species without significant bias and equally well, regardless of depth. The symbols for humans, rats, and pigs also appear to be randomly distributed about zero, suggesting the absence of systematic model distortion with respect to species for the multispecies models (Fig. 4*B*).

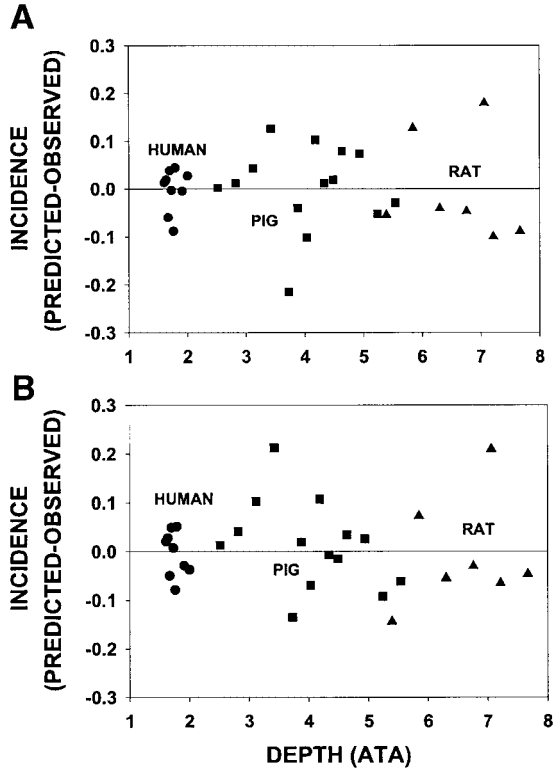

Fig. 4. Error for single-species (*A*) and multispecies models (*B*) are shown by plotting the difference between model prediction and observed incidence vs. saturation depth. Observed values are the mean incidence rates at each depth. Rat predictions were based on body weight set at 245 g, the mean weight of all rats. Both types of models predict DCS for a given species without significant bias and generally equally well, regardless of depth. Multispecies model also predicts across species without distortion.

The χ^2 tests of "goodness of fit" were also performed to provide a more formal evaluation of how well the models fit the data. However, two issues related to these tests need to be emphasized. First is the additional error introduced in the rat prediction due to body weight as just discussed. Second is the tendency to rely too strongly on such tests when arbitrary categorization is used. As discussed previously in some detail (19), outcomes of χ^2 tests can be highly dependent on the choice of categorization and, therefore, should be used only as a rough guide to identify problem areas of fit. Because the three species appeared to be the most logical breakdown of the data to examine model performance, the χ^2 tests were used to evaluate the ability of the single-species and multispecies models to predict DCS within each species. The test statistics were calculated for each species by using the 9 saturation depths for humans, 14 depths for pigs, and 7 depths for rats. The human, pig, and rat test statistics were found to be 8.7, 4.9, and 33.3 for the single-species models and 7.6, 4.8, and 47.6 for the multispecies model, respectively. According to this test, both models fit the human and pig data ($P > 0.05$), but both failed to fit the rat data ($P < 0.05$). However, the failure of the test for the rat predictions was not surprising, because of the effect of body weight, and should not be interpreted as an obvious failure of the model.

DISCUSSION

Multispecies models were developed in this study that allowed the sharing of common parameters among the three species. By employing one, more precise Hill equation exponent, the multispecies models allowed human risk predictions with smaller confidence limits compared with our human-only models. The predictions of the multispecies model agreed more closely with the observed data at 2 ATA, compared with the present US Navy model (USN93), although the confidence limits of both models overlapped those of the data. Thus it was impossible to declare one model better than the other at this depth, a situation that is very common in the field of risk prediction of DCS. However, it would not have been surprising if our relatively simplistic models, which were fit to data only from air-saturation, direct-ascent dives, improved prediction over more complex models such as USN93 that were fit to, and used to predict risk for, a wide variety of profiles.

The benefit of combining species, in terms of reducing the confidence limits of model predictions for human prediction, was relatively modest within the region in which human data are available. The real value of our approach becomes evident when extrapolation is necessary, and the addition of animal data is essential to make predictions without huge uncertainties. This was demonstrated when animal data were added to the abridged human data set, which was missing the dives at the two deepest depths. The addition restored the ability to resolve risk predictions for these two depths from zero. Unfortunately, we cannot presently determine the reliability of our predictions for depths greater than these. Consequently, the accuracy of our approach for human prediction awaits further experience and testing with other types of data, as has often been the case with the introduction of other new predictive models for DCS. However, it is this unique ability to predict human outcome, where no data are available, that is the primary goal of animal-to-human modeling. Certainly, any future work should focus on whether our conclusions regarding combining data hold true for other species and other types of dive profiles, such as those involving nonsaturation exposures or decompression stops.

The use of a common exponent in our multispecies models was based on the inability to resolve exponents among the individual species at least partly because of their large confidence limits, rather than very close agreement in their actual values. In a sense, by combining species, we have "merely" increased the number of observations used to calibrate a model for subsequent predictions of a human response. More observations lead to better predictive precision by well-established statistical principles. However, the additional subjects were "small" laboratory animals, not humans, illustrating one way that animal data might be of value in developing human decompression procedures. Such an approach translating animal models to human prediction could conceivably allow initial development of human procedures by using limited animal dives, while eliminating many human trials.

With the multispecies models, we are able to adjust the dose-response curve of any one of the three species to derive the curves of the other two by changing a single parameter, P_{50}. Because of the nature of the Hill equation, the steepness of any plotted dose-response curve depends on both the exponent and the dose range selected for the plot. Thus the multispecies curves show decreasing steepness going from human to pig to rat, despite having the same exponent, reflecting the larger magnitudes of dose at the greater saturation depths. A more detailed evaluation of the contribution of the P_{50} and exponent to these combined-species models would, in our opinion, push the interpretation of the parameters beyond what appears warranted, in view of the relative imprecision associated with these (e.g., Fig. 4) and other decompression models.

The simple profiles used in this study allowed any differences in gas kinetics to be ignored. However, a previous study defining risk of DCS in humans and sheep needed to include parameters explicitly defining gas kinetics, because bottom times were ≤3 h (1). That study reported that separate gas-exchange parameters

Table 5. *Effect of scoring criteria on model parameters*

Scoring Criteria	Species	Separate	Combined
	P_{50}		
No human marginals/animal DCS*	Human	1.05 ± 0.06	1.11 ± 0.06
	Pig	3.03 ± 0.09	2.97 ± 0.11
	Rat	4.74 ± 0.18	4.93 ± 0.10
With human marginals/animal DCS	Human	0.95 ± 0.05	0.94 ± 0.03
	Pig	3.03 ± 0.09	2.95 ± 0.12
	Rat	4.74 ± 0.18	4.87 ± 0.11
No human marginals/animal death	Human	1.05 ± 0.06	1.03 ± 0.04
	Pig	3.63 ± 0.10	3.67 ± 0.10
	Rat	5.65 ± 0.06	5.64 ± 0.06
	Exponent		
No human marginals/animal DCS*	Human	7.90 ± 1.75	6.42 ± 0.83
	Pig	8.67 ± 2.30	6.42 ± 0.83
	Rat	4.67 ± 1.05	6.42 ± 0.83
With human marginals/animal DCS	Human	5.39 ± 1.15	5.75 ± 0.72
	Pig	8.67 ± 2.30	5.75 ± 0.72
	Rat	4.67 ± 1.05	5.75 ± 0.72
No human marginals/animal death	Human	7.90 ± 1.75	8.64 ± 0.94
	Pig	10.62 ± 2.32	8.64 ± 0.94
	Rat	8.29 ± 1.29	8.64 ± 0.94
	Weight factor		
No human marginals/animal DCS*	Rat	2.58 ± 0.59	2.00 ± 0.31
With human marginals/animal DCS	Rat	2.58 ± 0.59	2.17 ± 0.34
No human marginals/animal death	Rat	1.03 ± 0.19	1.01 ± 0.17

Values are parameter estimates ± SE for Hill equation models fit to all 3 species separately or combined, with the specific scoring criteria noted. *These results, previously given in the main body of the paper, are provided for comparison.

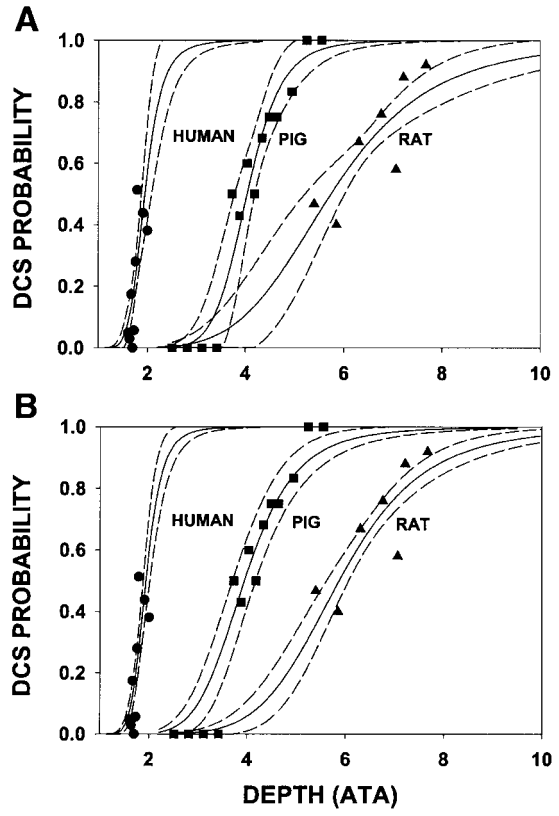

Fig. 5. Alternative scoring criteria for DCS: human marginals included, all animal DCS (including death). Predictive curves (solid lines) [and 95% confidence belts (dashed lines)] for single-species (*A*) and multispecies models (*B*) relating decompression risk to saturation depth for direct-ascent air dives are shown for the 3 species. Symbols represent actual data with mean incidence rate of DCS calculated for each depth. Rat predictions were based on body weight set at 245 g, the mean weight of all rats.

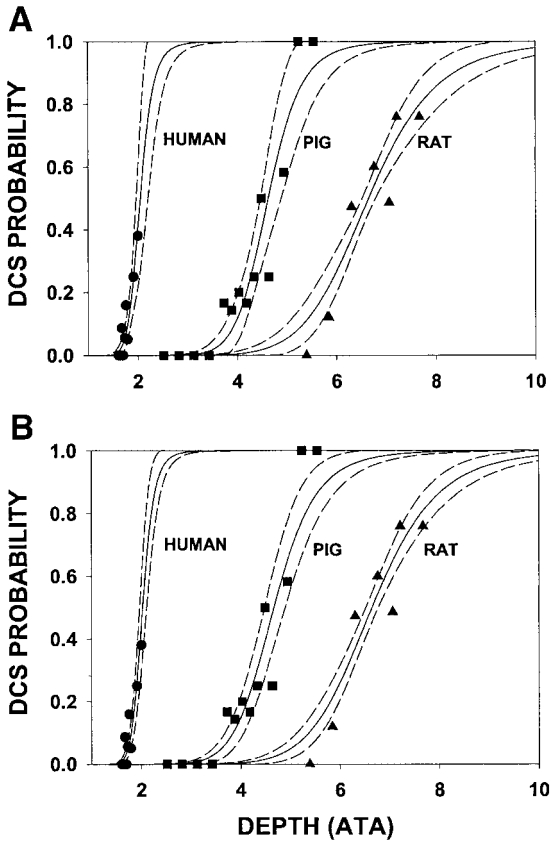

Fig. 6. Alternative scoring criteria for DCS: human marginals excluded, animal death only. Predictive curves (solid lines) [and 95% confidence belts (dashed lines)] for single-species (*A*) and combined species models (*B*) relating decompression risk to saturation depth for direct-ascent air dives are shown for the 3 species. Symbols represent actual data with mean incidence rate of DCS calculated for each depth. Rat predictions were based on body weight set at 245 g, the mean weight of all rats.

for humans and sheep were not statistically warranted, allowing common parameters to be estimated from the combined data with reduced error, as was the case here. Those adjustments for species are analogous to the adjustments in P_{50} required in the present work and provide precedent for our work, although their risk-based models are very different from our Hill equation models.

The elevated risk of DCS with increasing weight within a species was confirmed in rats, although not in pigs in this study. Thus an intraspecies weight correction for DCS risk can be very important and potentially large. In the illustration presented earlier (Fig. 2), a remarkable increase of ~1% in DCS risk was estimated for each gram increase of rat weight, which agrees with observations made for rats over 15 yr ago, subjected to saturation dives with multiple inert gases (12). Unfortunately, there was no attempt to incorporate sheep weight into the previously reported combined human and sheep model of decompression risk, despite a fivefold range in weight of the animals (1).

As expected, the additional analyses in the APPENDIX show that the parameter estimates were affected by the specific scoring criteria for DCS selected for the model. Thus the adjustment in P_{50} for interspecies predictions reflects differences not only in tolerance to decompression, but also in scoring criteria. However,

Table 6. *Effect of scoring criteria on predictions by Hill multispecies model*

Scoring Criteria	DCS, %		
	2.00 ATA	2.21 ATA	2.52 ATA
No human marginals/animal DCS*	34(21–47)	64(46–82)	88(77–100)
With human marginals/animal DCS	59(48–71)	82(71–92)	94(89–100)
No human marginals/animal death	44(30–59)	81(68–94)	97(93–100)

Predictions are for human DCS after air saturation at 3 depths, followed by direct ascent to the surface. The 95% confidence limits for the predictions are in parentheses. *These results, previously given in the main body of the paper, are provided for comparison.

regardless of which of the three sets of definitions of DCS was used, the multispecies models agreed in terms of *1*) a common Hill equation exponent for all three species and *2*) the relative magnitude of the precision associated with the parameter estimates. This occurred despite the fact that the degree of overlap of incidence levels among species varied with how DCS was defined. Indeed, the multispecies models did not seem to be affected by whether there was little data overlap among species (as with humans and rats in Fig. 1) or considerable overlap (as in Fig. 6). These findings are encouraging to any future efforts where there may be differences in symptoms and incidence levels of DCS among species.

We would caution against immediate rejection of our approach of combining animal and human data simply because animal DCS in many cases is more severe than that in humans and, therefore, appears "different" from the average human case. Within any human data set, there is normally also a range in symptoms and severity among DCS cases, particularly when working with a variety of different types of profiles (21). Among species, there certainly are differences in tolerance to decompression, with relative susceptibility to DCS tending to increase with species size (2, 7). One common explanation for these differences is that higher metabolism, with accompanying faster circulation, hastens gas elimination in smaller animals. However, others have suggested that small animals may also be better able to cope with an excess amount of gas and avoid DCS (9). On the basis of the strong relationship between body weight and DCS susceptibility, Flynn and Lambertsen (7) suggested that species differences probably reflect differences in susceptibility to DCS rather than a fundamental difference in the nature of DCS among animals. Interestingly, Lin (16) concluded from Doppler experiments that the maximum change in pressure without forming intravascular bubbles was the same in rats, cats, and dogs with the use of rapid decompression rates designed to minimize any gas off-loading. These observations suggest that response differences among species to the insult of decompression may reflect a combination of factors, including differences in gas exchange and tolerance to excess gas in the body.

APPENDIX

Changes in Scoring Criteria

Other data sets were modeled by using the Hill equation to examine the robustness of our results relative to changes in the scoring criteria to define DCS. Fitting methods were identical to those described for the main model. The changes in scoring criteria consisted of *1*) including all marginal cases of DCS for humans and *2*) excluding all DCS cases for animals except those that resulted in death. Predictive models were developed separately for each species by using the alternate definitions of DCS. Two additional multispecies models were created: *1*) human DCS (including marginals) and pig and rat DCS; and *2*) human DCS (no marginals) and pig and rat death. No multispecies model was fit to a data set, which included human marginals and defined animal DCS as death, to avoid combining such extremely different responses.

Although we had hoped to model central nervous system (CNS) DCS in humans, our review of the 21 cases of DCS in our human data revealed only two (perhaps 3) cases of CNS DCS. Modeling human CNS DCS and treating only these three cases as positive DCS outcomes produced estimates for the P_{50} of 1.23 (SE = 0.20) and for the exponent of 10.8 (SE = 5.6). These results, particularly for the exponent error, confirmed our expectation that the small number of CNS cases prevented reliable estimation of parameters. As a result, human CNS DCS was not modeled separately in this study.

As would be expected, including marginals in the definition of human DCS affected the P_{50} estimate, although the 95% confidence limits (2 SEs) of the P_{50} values, with and without marginals, overlapped (Table 5). For pigs and rats, the P_{50} values for the death response were higher than those for DCS, as a greater saturation depth was required to produce fatalities. The specific predictions (and confidence limits) for the multispecies models were also somewhat different from those for the single-species models and depended on the scoring criteria. This is evident by comparing the plotted curves in Figs. 1, 5, and 6 and the risk predictions in Table 6. However, it was impossible to resolve any difference between using animal DCS or death for predicting human risk.

This work was supported by funding from the Deep Submergence Biomedical Development Program.

REFERENCES

1. **Ball R, Lehner CE, and Parker EC.** Predicting risk of decompression sickness in humans from outcomes in sheep. *J Appl Physiol* 86: 1920–1929, 1999.
2. **Berghage TE, David TD, and Dyson CV.** Species differences in decompression. *Undersea Biomed Res* 6: 1–13, 1971.
3. **Berghage TE and McCracken TM.** Equivalent air depth: fact or fiction. *Undersea Biomed Res* 6: 379–384, 1979.
4. **Boycott AE, Damant GCC, and Haldane JS.** Prevention of compressed air illness. *J Hyg Lond* 8: 342–443, 1908.
5. **Dromsky DM, Toner CB, Survanshi S, Fahlman A, Parker E, and Weathersby P.** Natural history of severe decompression sickness after rapid ascent from air saturation in a porcine model. *J Appl Physiol* 89: 791–798, 2000.
6. **Edwards AWF.** *Likelihood.* London: Cambridge Univ. Press, 1972.
7. **Flynn ET and Lambertsen CJ.** Calibration of inert gas exchange in the mouse. In: *Proceedings of the Fourth Symposium on Underwater Physiology,* edited by Lambertsen CJ. New York: Academic, 1971, p. 179–191.
8. **Kendall MG and Stewart A.** *The Advanced Theory of Statistics* (4th ed.). London: Haffner, 1979, vol. 2, p. 38–180.
9. **Kindwall EP.** Metabolic rate and animal size correlated with decompression sickness. *Am J Physiol* 203: 385–388, 1962.
10. **Ku HH.** Notes on the use of propagation of error formulas. *J. Res Natl Bur Stand Eng Instr* 70C: 263–273, 1966.
11. **Lillo RS.** Effect of N_2-He-O_2 on decompression outcome in rats after variable time-at-depth dives. *J Appl Physiol* 64: 2042–2052, 1988.
12. **Lillo RS, Flynn ET, and Homer LD.** Decompression outcome following saturation dives with multiple inert gases in rats. *J Appl Physiol* 59: 1503–1514, 1985.
13. **Lillo RS and MacCallum ME.** Decompression comparison of N_2 and O_2 in rats. *Undersea Biomed Res* 18: 317–331, 1991.
14. **Lillo RS and MacCallum ME.** Effect of inert gas switching at depth on decompression outcome in rats. *J Appl Physiol* 67: 1354–1363, 1989.
15. **Lillo RS and Parker EC.** Mixed-gas model for predicting decompression sickness in rats. *J Appl Physiol* 89: 2107–2116, 2000.

16. **Lin YC.** Species independent maximum no bubble pressure reduction from saturation dive. In: *Proceedings of the Seventh Symposium on Underwater Physiology*, edited by Bachrach AJ and Matzen MM. Bethesda, MD: Undersea Med. Soc., 1981, p. 699–705.
17. **Lin YC, Shidara F, Tara Y, Mizushima Y, and Mohri M.** Interspecies conversion of tables for decompression from 300 msw (UDT3000). In: *Basic and Applied High Pressure Biology,* edited by Bennett PB and Marquis RE. Rochester, NY: University of Rochester Press, 1994, p. 342–352.
18. **Marquardt DW.** An algorithm for least-squares estimation of non-linear parameters. *J Soc Ind Appl Math* 11: 431–441, 1963.
19. **Parker EC, Survanshi SS, Massell PB, and Weathersby PK.** Probabilistic models of the role of oxygen in human decompression sickness. *J Appl Physiol* 84: 1096–1102, 1998.
20. **Survanshi SS, Parker EC, Thalmann ED, and Weathersby PK.** *Statistically Based Decompression Tables XII. Repetitive Decompression Tables for Air and Constant 0.7 ATA PO_2 in N_2 Using a Probabilistic Model.* Bethesda, MD: Naval Medical Research Institute, 1997, vol. 1. (NMRI Rep. 97-36)
21. **Temple DJ, Ball R, Weathersby PK, Parker EC, and Survanshi SS.** *The Dive Profiles and Manifestations of Decompression Sickness Cases after Air and Nitrogen-Oxygen Dives.* Bethesda, MD: Naval Medical Research Center, 1999. (NMRC Rep. 99-02)
22. **Thalmann ED, Parker EC, Survanshi SS, and Weathersby PK.** Improved probabilistic decompression model risk predictions using linear-exponential kinetics. *Undersea Hyperb Med* 24: 255–274, 1997.
23. **Weathersby PK, Homer LD, and Flynn ET.** On the likelihood of decompression sickness. *J Appl Physiol* 57: 815–825, 1984.
24. **Weathersby PK, Survanshi SS, Parker EC, Temple DJ, and Toner CB.** *Estimated DCS Risks in Pressurized Submarine Rescue.* Bethesda, MD: Naval Medical Research Center, 1999. (NMRC Rep. 99-04)