Modeling pulmonary and CNS O_2 toxicity and estimation of parameters for humans

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Arieli, R., A. Yalov, and A. Goldenshluger. Modeling pulmonary and CNS O_2 toxicity and estimation of parameters for humans. J Appl Physiol 92: 248–256, 2002; 10.1152/japplphysiol.00434.2001.—The power expression for cumulative oxygen toxicity and the exponential recovery were successfully applied to various features of oxygen toxicity. From the basic equation, we derived expressions for a protocol in which P02 changes with time. The parameters of the power equation were solved by using nonlinear regression for the combined data, yielding the power equation for active diving (the combined data, yielding the power equation for active diving).

The parameters of the model were solved for any form of oxygen toxicity. We subsequently applied the model to various cases of oxygen toxicity, including pulmonary oxygen toxicity, CNS oxygen toxicity, and recovery. It is suggested that the risk of CNS oxygen toxicity in diving can be derived from the calculated parameter of the normal distribution: Z = ln(t) - 9.63 + 3.38 × ln(P02/101.3)/20.2. The recovery time constant for CNS oxygen toxicity was calculated from the value obtained for the rat, taking into account the effect of body mass, and yielded the recovery equation: K(t) = K_e × e^{-0.07t}, where K_e and K_t are the values of K at time t of the recovery process and at the end of the hyperoxic oxygen exposure, respectively, and t is in minutes.

Hyperoxic oxygen; pulmonary oxygen toxicity; central nervous system oxygen toxicity

Hyperbaric oxygen (HBO) is encountered in clinical treatment in the hyperbaric chamber and in diving. The risk of oxygen toxicity became a prominent issue with the increased use of hyperbaric treatment and the expansion of diving techniques to include oxygen-enriched gas mixtures. However, there is no satisfactory method of calculating the cumulative risk of oxygen toxicity during a HBO exposure. There have been various attempts to quantify the risk of pulmonary oxygen toxicity (9, 15) and central nervous system (CNS) oxygen toxicity. A recent approach of Harabin et al. (18) was to process, in one equation, developing CNS oxygen toxicity, recovery, and the P02 threshold (with the assumption being that any specified form of oxygen toxicity will not develop below the specified P02 threshold). However, the toxic process of HBO could differ widely from the recovery process. The toxic process itself, non-steady-state production of reactive oxygen species (ROS) and increased injury, may differ from the steady-state production and removal of ROS, which is the normal state and in which recovery may occur. Therefore, one should not expect that one equation might be applicable to all conditions: developing toxicity, steady state, and recovery. It is not surprising, therefore, that such analyses fail to solve the threshold P02, when the parameters of an equation describing both oxygen toxicity and the threshold are solved simultaneously for pulmonary oxygen toxicity (15) and for CNS oxygen toxicity (17). During the past few years, we have developed a quantitative approach to both the toxic process (a power expression) and the exponential recovery (1–3, 6, 7, 22) for the various forms of oxygen toxicity in animals and humans. This approach has been used satisfactorily to interpret various published data and successfully employed to predict the outcome of HBO exposures on CNS oxygen toxicity (6, 7). Because the possibilities of exposing humans to toxic levels of oxygen are limited, our present strategy is to discover the laws of oxygen toxicity in other mammals and to apply them with the appropriate parameters in humans. Some parameters can be derived from human data, and others, by allo- metric extrapolation, can be derived from other mammals. The main body of data for CNS oxygen toxicity has been derived from the rat, and studying a larger mammal may help refine the parameters selected for humans.

In the present report, we shall introduce the general power equation for any form of oxygen toxicity. We shall continue with a description of its two facets for measurable damage and for all-or-none effects. A description of the exponential recovery will follow. Parameters will be suggested for the reduction in vital capacity (VC), as one example of measurable damage of...
oxygen toxicity. Parameters will also be suggested for CNS oxygen toxicity, as one example of the all-or-none phenomena. To conclude, we shall propose hyperoxic exposure limits for humans.

**QUANTITATIVE EXPRESSIONS FOR OXYGEN TOXICITY**

**Quantification Principles**

We assumed that an oxygen-damaged measurable physiological variable (DMG) may have the same relationship with time \( t \) and \( PO_2 \) as the ROS that caused the damage (2). We formulated equations for the kinetics of the main ROS by assuming a non-steady state where the action of scavengers is negligible. On the basis of these equations and the published data on various forms of oxygen toxicity, we propose our two power equations

\[ \text{Eq. 1} \]

\[ \text{Eq. 2} \]

\( K = t^2 PO_2^c \) (2)

where \( K \) is the cumulative oxygen toxicity index. A symptom may appear when \( K \) reaches a threshold value \( K_c \). Each form of all-or-none oxygen toxicity would have a different \( c \) and \( K_c \). These power equations agree with various phenomena of oxygen toxicity (2, 3), and it was proven possible to use the algorithm derived (3) to predict CNS oxygen toxicity in the rat as a result of a complex HBO exposure (6, 7).

**Complex Exposures**

For a complex exposure profile at toxic levels of oxygen, it can be shown (APPENDIX A, Eqs. A2–A5) that the cumulative oxygen toxicity indexes, either the parametric DMG or the nonparametric \( K \), follow simple algorithms. In a stepwise exposure [a definite number of intervals \((n)\), each having a selected \( PO_2 (PO_2_i) \) and exposure duration \((t_i)\)]

\[ \text{DMG} = a \left( \sum_{i=1}^{n} [t_i \times PO_2^{(2i)}] \right)^2 \] (3)

\[ K = \sum_{i=1}^{n} [t_i \times PO_2^{(2i)}] \] (4)

For an exposure in which there is a continuous change in \( PO_2 \) with time, the indexes are solved for their integral forms

\[ \text{DMG} = a \left( \int_0^{t_{ox}} PO_2^{(2i)} dt \right)^2 \] (5)

\[ K = \left( \int_0^{t_{ox}} PO_2^{(2i)} dt \right)^2 \] (6)

where \( t_{ox} \) is the exposure time at a toxic level of oxygen.

**Recovery Equations**

The power equation, which was developed by using the non-steady-state production of ROS, is valid in this toxic \( PO_2 \) range. We speculate that, below the toxic level, there could be a neutral level (mostly undefined) at which toxicity ceases to develop any further but at which there is still no recovery either. Below this speculated neutral \( PO_2 \) range is the range in which recovery from the toxic effect takes place. When the complex exposure also contains a nontoxic \( PO_2 \), it is possible to make a recovery calculation.

It has been suggested that recovery from oxygen toxicity in normoxia follows an exponential function for both oxygen toxicity damage and for all-or-none effects (3, 22)

\[ \text{DMG}_t = \text{DMG}_e \times e^{-rt} \] (7)

and

\[ K_t = K_e \times e^{-rt} \] (8)

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where $DMG_t$ and $K_t$ are the values of the toxicity indexes at time $t$ of the recovery process, $DMGe$ and $Ke$ are the values at the end of the hyperoxic exposure, and $\tau$ is the recovery time constant. Different manifestations of oxygen toxicity will each have an appropriate time constant. This approach could well describe the recovery of the hypoxic ventilatory drive in rats and the recovery of human VC (22, 13), and, together with the power equation, it has been used successfully to predict recovery from CNS oxygen toxicity in rats when intermittent exposure is used (6).

**SELECTING THE PARAMETERS FOR HUMANS**

Because the basic processes of toxicity and recovery are common to all mammals, the power equation and the recovery function can be applied to humans with the appropriate parameters, $a$, $c$, $K_a$, and $\tau$, and the variability within each parameter. Two limits of oxygen toxicity are set for human exposure: one related to pulmonary oxygen toxicity and expressed by the reduction in VC, and the other for CNS oxygen toxicity.

**Pulmonary Values**

There are enough data to derive the parameters for pulmonary oxygen toxicity in the equation $DMG = a \times t^2(PO_2/101.3)^c$. From the data of Clark et al. (11, 12) and Eckenhoff et al. (13), the solved parameters using nonlinear regression are $a = 0.0082$ and $c = 4.57$, where $DMG = \%DVc$ (where $\Delta VC$ is the reduction in VC), time $t$ is expressed in hours, and $PO_2$ in kPa. The mean data from those studies, together with the lines solved by the power equation, are shown in Fig. 1. From the data of Eckenhoff et al. (13) and Clark et al. (12), $\tau$ was 0.0128, 0.1047, 0.3740, and 0.5437 h$^{-1}$ for $PO_2$ values of 106, 152, 203, and 253 kPa, respectively. Recovery of VC, together with the lines representing the exponential solution, is shown in Fig. 2. When the values obtained for $\tau$ were plotted as a function of the $PO_2$ in the preceding hyperoxic exposure, a linear relationship was obtained, such that $\tau = -0.420 + 0.00379 PO_2$ (Fig. 3). Therefore, the recovery of VC will take the form $\Delta VC = \Delta VC_e \times e^{-0.420 + 0.00379 PO_2}$. As with $DMGe$ in Eq. 7, $\Delta VC_e$ is the reduction in VC at the end of the hyperoxic exposure.

In developing our approach to recovery, we assumed that recovery depends on the level of injury, regardless of the time and $PO_2$ that caused this injury. This will be true if identical injury levels have the same rate of recovery, irrespective of how they were produced. It is not surprising, however, that the rate of recovery depends on the $PO_2$ that caused the loss of VC. For the same decrement in VC, other symptoms differed. Severity of pulmonary symptoms (chest pain, cough, chest tightness, and dyspnea) was greater during exposure to 152 and 203 kPa than to 253 and 304 kPa, neutrophil count was greater after 152 kPa than after the 203-kPa exposure, and postexposure arterial $PO_2$ during exercise dropped after exposure to 152 kPa but...
not after exposure to 203 or 253 kPa (12). Thus, for the same decrement in VC, the deleterious effects on the lung are related to the pressure at which the insult occurred.

The US Navy recommended oxygen exposure limits that would result in a 2% change in VC and a maximum exposure expected to produce a 10% decrement (20). Thus inserting ΔVC = 2% or ΔVC = 10% into the power equation will set the P02 and time limits, and the value of \( t^2(PO_2/101.3)^{5.62} \) at a constant pressure or the cumulative value in a complex exposure should not exceed the values 244 and 1,220, respectively.

**CNS Oxygen Toxicity Values**

**Background. Power Equation and Recovery.** For CNS oxygen toxicity, the data for convulsions in humans are not sufficient for derivation of the parameters, and the parameters for other models were derived from symptoms other than convulsions (17). We used our data from rats carefully acclimated to the hyperbaric chamber in air, with the maintenance of thermoneutral conditions and a lack of CO2, to derive the parameters \( c = 5.61 \) (SE = 0.35) and \( K_c = 5.36 \times 10^6 \) (SE = 3.18 \times 10^6) \( n = 290, \) \( PO_2 \) range 456–810 kPa, data collected between 1994 and 1999). The mean data and the line representing the prediction of the model are shown in Fig. 4. For the rat, the mean \( τ = 0.31 \) min\(^{-1}\), and thus 95% recovery is achieved within 10 min (6).

**Modulators of CNS Oxygen Toxicity.** The two principal modulators affecting CNS oxygen toxicity are metabolic rate and CO2 load (4, 5). The quantification of these effects was recently studied by us in the rat. We believe that this form of response is common to various mammals with the appropriate parameters. If the power \( c \) does not change with alterations in metabolic rate or CO2, these will be reflected in \( K_c \).

For the metabolic rate effect, CNS oxygen toxicity will develop faster during exercise or when metabolic rate is elevated. This metabolic rate-induced increase in the risk of CNS oxygen toxicity probably involves other known factors, such as cold exposure and high levels of thyroxine (4). We postulated that, at a constant \( PO_2 \), the latency to CNS oxygen toxicity decreases linearly as CO2 production [or oxygen consumption (\( VO_2 \))] increases (4) (Fig. 5, right). It is possible to derive \( K_c \) at rest (\( K_{c0} \)) and at an increased metabolic rate (\( K_{cex} \)). From our experiment, the latency to CNS oxygen toxicity \( t = A - B \cdot VO_2 \). Inserting this relationship into the power equation yields (\( K_{cex} \)) = \( t^2 \cdot PO_2 = (A - B \cdot VO_2)P_2 \). Therefore the ratio

\[
K_{cex}/K_c = [(A - B \cdot VO_2)/(A - B \cdot VO_2)]^2
\]

where \( VO_2 \) and \( VO_2 \) are \( VO_2 \) at increased metabolic rate and at rest, respectively. As metabolic rate increases, \( K_c \) decreases, which means that the symptoms will appear at a lower combination of time and oxygen pressure. We have shown that both \( A \) and \( B \) are a function of \( PO_2 \)

\[
A = e^{A_1 - B_1 \times PO_2}
\]

and

\[
B = e^{A_2 - B_2 \times PO_2}
\]

Therefore, both parameters \( A \) and \( B \) decrease with the increase in \( PO_2 \).

For the CO2 effect, an increased level of CO2 in the inspired gas accelerates the development of CNS oxygen toxicity in humans, as well as in other mammals such as the cat, the rat, and the mouse (5). We have shown in rats that, at a constant toxic \( PO_2 \), latency to CNS oxygen toxicity decreases linearly with the increase in inspired \( PCO_2 \), down to a latency level from which there is no further reduction in latency with any further increase in \( PCO_2 \) (Fig. 5, left). At a constant toxic \( PO_2 \) in the \( PCO_2 \)-dependent range, \( t = C - D \times PCO_2 \). Replacing \( t \) in the power equation will yield

\[
K_{cCO_2} = t^2 \cdot PO_2 = (C - D \times PCO_2)^2 \cdot PO_2 \]

where \( K_{cCO_2} \) is \( K_c \) at elevated \( PCO_2 \). From this expression, the ratio of \( K_c \) at elevated \( PCO_2 \) (\( K_{cCO_2} \)) to \( K_c \) at no CO2 (\( K_c \)) is as follows

\[
K_{cCO_2}/K_c = [(C - D \times PCO_2)/C]^2
\]

\( K_c \) decreases with the increase in inspired CO2. Both \( C \) and \( D \) are a function of \( PO_2 \)

\[
c = e^{C_1 - D_1 \times PO_2}
\]

and

\[
D = e^{C_2 - D_2 \times PO_2}
\]

Therefore, both parameters \( C \) and \( D \) decrease with the increase in \( PO_2 \). At higher \( PCO_2 \) values, when latency to CNS oxygen toxicity is reduced but remains constant despite any further increase in \( PCO_2 \), it was found in rats that latency to CNS oxygen toxicity \( t = e^{C_3 - D_3 \cdot PO_2} \). The ratio of \( K_c \) at the maximal effect of CO2 (\( K_{cCO_2,ex} \)) to \( K_c \) is

\[
K_{cCO_2,ex}/K_c = (e^{C_3 - D_3 \cdot PO_2}/t)^2
\]

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where the term on the left is always positive and lower than 1.

VARIABILITY. Our laboratory has shown that there is individual sensitivity to CNS oxygen toxicity in the rat, so that the variability within the rat is much less than the variability between rats (4–7). The prediction of CNS oxygen toxicity based on individual parameters proved superior to employing the group means (7). The issue of individual sensitivity in humans has not been settled yet. Butler and Thalmann (10) suggested that there may be a small number of divers sensitive to CNS oxygen toxicity, although Harabin et al. (16) failed to prove this. However, there are no studies in humans that can be compared with the rat data, which provided clear evidence of individual sensitivity.

RECOVERY TIME CONSTANT IN HUMANS. Because measurements were not made in any other mammals, it would only be reasonable to guess that the use of body mass (BM) might provide us with an approximate solution to the problem. The rate of various physiological processes in mammals (19) is related to BM to the power 20.25. Therefore, the time for 95% recovery in humans should be 10(BMrat/BMhuman)−0.25 = 39 min, and ηhuman = τrat (BMrat/BMhuman)−0.25 = 0.079 min−1, where BM is rat BM, BMhuman is human BM, η is human η, and τ is rat τ. It is interesting to note that our suggestion agrees with the “rule of thumb” used by Israeli combat divers. Thus, for toxic exposures interspersed with periods of nontoxic PO2, the reduction in the value of K can be evaluated by using the suggested time constant. Although this time constant was derived from the value measured for the rat, no better approach is available at present.

CNS parameters in humans. The parameters for the power equation can be derived by using the maximum likelihood method for censored observations (APPENDIX B). We extracted those data used by Harabin et al. (17) for exposure to a constant PO2 from all of the data in Harabin’s collection (Ref. 14, p. 96–136, compiled from eight different reports, mostly the work of Butler FK and Thalmann ED). The data obtained were from 661 exposures with 3.6% CNS oxygen toxicity symptoms as defined by Harabin et al. (17).

For comparison, we applied the same analysis of CNS oxygen toxicity to our rat data. To the data (n = 290) used for derivation of the power equation parameters for rats, we added exposures to low PO2 when only some rats experienced CNS oxygen toxicity. Thus for a PO2 range of 253–810 kPa, the total data included 395 exposures with 73% CNS oxygen toxicity. The parameters solved for the rat were c = 6.8 (SE = 0.2) and Kc = 6.7 × 107, P < 0.0001 χ2 for both parameters. The power of PO2 with the data for the 395 exposures, including the low PO2 values, was higher by 1.2 than the value calculated for the data for the 290 exposures for the high PO2 values.

The parameters solved by using the model for human hyperbaric exposures were c = 15.0 (SE = 1.8) and Kc = 5.28 × 109 (P < 0.0001 χ2 for both parameters and σ = 1.35). The risk for CNS oxygen toxicity was calculated by using Eq. B3 in APPENDIX B for the normal distribution

\[ Z = \left[ \ln(t) - 11.193 + 7.475 \ln \left( \frac{\text{PO}2 /101.3}{\text{PO}2 /101.3} \right) \right] / 1.35 \]  

The calculated risk is shown in Fig. 6 as a function of time and PO2 at 1-m depth intervals.

![Fig. 5. Latency to CNS oxygen toxicity in the rat as a function of PCO2 and PO2 (left) and as a function of CO2 production (VCO2) and PO2 (right). The exposure PO2 in kPa is indicated next to the line by which it is represented.](http://jap.physiology.org/)

![Fig. 6. Percent risk of CNS oxygen toxicity as a function of time and PO2. The parameters for the calculation were derived from human hyperbaric exposures (14).](http://jap.physiology.org/)
We gathered reports of 2,039 closed-circuit oxygen dives from the Israel Navy SEALs. The dives were active training fin dives in the Mediterranean Sea throughout the year at water temperatures ranging from 17 to 28°C. After each dive, the diver completed a form reporting the dive profile and marked a list of symptoms, if any. We measured 98% oxygen concentration in the inspired gas in samples taken during the dives after a few purging procedures and a V\(_\text{O}_2\) of 1.4 l/min. Mean depth was 4.2 ± 0.1 (SD) m, and duration was 109 ± 54 (SD) min. Although the percentage of symptoms related to CNS oxygen toxicity in the diving data (3.5%) was similar to that found for the hyperbaric experiments, the maximum likelihood analysis did not yield significant results \(\chi^2\) for a slope of \(-c/2\) vs. ln(P\(_O2\)) was not significant, \(P = 0.93\). This may be related to the low range of P\(_O2\) (132–162 kPa) for the diving data compared with the hyperbaric experiments (160–250 kPa). We, therefore, took the data from the hyperbaric exposures together with the diving data and applied the maximum likelihood method. The parameters solved using the model for the combined data were \(c = 6.8\) (SE = 1.25) and \(K_c = 2.31 \times 10^8\) (\(P < 0.0001\) \(\chi^2\) for both parameters and \(\sigma = 2.02\)). The calculation of the normal distribution will now be

\[
Z = \frac{[\ln(t) - 9.63 + 3.38 \times \ln(\text{P}\_O2/101.3)]/1.35}{17}
\]

It is interesting that the same power \(c\) (6.8) was solved for both rats and humans. This may be indicative of a similar process.

For each diving depth, we calculated the percentage of symptoms during 1-h intervals. The percentage of dives with symptoms during the first hour was added to that for the next hour, and so forth, for calculation of the cumulative risk. This cumulative percentage of CNS oxygen toxicity-related symptoms is shown in Fig. 7, represented by solid circles. We used Eq. 16 (Fig. 7, open circles) and Eq. 17 (Fig. 7, open squares) to calculate the risk. The calculated risk using the parameters derived from the hyperbaric experiments is much lower than the actual percentage of symptoms. Underestimation of the calculated risk is also evident in the calculation using parameters from both diving and hyperbaric exposures, but in this case the risk is closer to the actual data.

The dives were active training dives, in which \(\text{V}\_O2\) was \(\sim 1.4\) l/min (8). This \(\text{V}\_O2\) is higher than that in the hyperbaric experiments, in which 6 min of exercise (1.3 l \(\text{O}_2\)/min) were followed by 4 min of rest (17). This protocol would yield a mean \(\text{V}\_O2\) of 0.9 l/min. The weighted mean \(\text{V}\_O2\) for both diving and experimental data is 1.28 l \(\text{O}_2\)/min. It is possible that the three lines in each of the panels in Fig. 7 represent the risk at three separate levels of \(\text{V}\_O2\).

We used our model with the parameters derived from the hyperbaric experiments and from diving and hyperbaric experiments taken together to calculate the risk within the suggested limits of the United States Navy Single \(\text{P}\_O2\) Diving Limits (21) (Fig. 8, Table 1). This calculated risk is higher than the calculated risk of Harabin et al. (17), mainly at 25 and 30 ft. When we calculated the time at which 5 or 10% of the divers will experience symptoms related to CNS oxygen toxicity (using both the parameters from the hyperbaric experiments and those
Table 1. Calculation of the risk of CNS oxygen toxicity within the limits suggested by the US Navy

<table>
<thead>
<tr>
<th>Depth, fsw</th>
<th>t, min</th>
<th>Risk Experiments, %</th>
<th>Risk Experiments + Dive, %</th>
<th>Experiments t for 5% risk, min</th>
<th>Experiments + Dive t for 10% risk, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>240</td>
<td>13.5</td>
<td>13.4</td>
<td>115</td>
<td>188</td>
</tr>
<tr>
<td>30</td>
<td>80</td>
<td>7.3</td>
<td>6.5</td>
<td>62</td>
<td>101</td>
</tr>
<tr>
<td>40</td>
<td>25</td>
<td>2.9</td>
<td>2.5</td>
<td>35</td>
<td>57</td>
</tr>
<tr>
<td>50</td>
<td>15</td>
<td>3.0</td>
<td>1.8</td>
<td>21</td>
<td>34</td>
</tr>
</tbody>
</table>

Columns 1 and 2, single PO2 diving limits (21). Parameters used for the model were derived from either hyperbaric experiments (14) or from our diving data and the hyperbaric experiments. The calculated percentage of divers who will experience central nervous system (CNS) oxygen toxicity symptoms is given in columns 3 and 4. The time (t) until either 5 or 10% of the divers will experience symptoms is presented in columns 5–8.

The damage after a second time interval \( t_2 \) will be

\[
DMG_2 = a(t_1' + t_2)^2PO_2^{22} = a(t_1' + t_2)PO_2^{23/2}
\]

Replacing \( t_1' \) by its value in Eq. A1, we obtain

\[
DMG_2 = a([t_1 PO_2^{22}]^2 + t_2 PO_2^{22}) = a[t_1 PO_2^{22} + t_2 PO_2^{22}]
\]

The time \( t_{2T} \) at PO2 that will yield DMG2 is

\[
t_{2T} = t_1' + t_2 = t_1 (PO_2/PO_2^{22})^{22} + t_2
\]

\[= t_1 (PO_2/PO_2^{22})^{22} + t_2 (PO_2/PO_2^{22})^{22}
\]

The expressions

\[
DMG_n = a \left( \sum_{i=1}^{n} t_i PO_2^{22} \right)^2
\]

and

\[
t_{nT} = \sum_{i=1}^{n} t_i (PO_2/PO_2^{22})^{22}
\]

hold for \( n = 2 \). Let us assume that this is true for \( n \) steps and prove that it is true for \( n + 1 \).

Let us define \( t_n' \) as the time at \( PO_2^{22}+1 \) that will produce DMGn. Then

\[
DMG_n = at_n'^2PO_2^{22} = at_n'^2PO_2^{22}+1
\]

from which it follows that

\[
t_n' = t_{nT}(PO_2/PO_2^{22})^{22}
\]

and

\[
t_{n+1T} = t_n' + t_{n+1}
\]

\[
= \sum_{i=1}^{n} t_i (PO_2/PO_2^{22})^{22} + t_{n+1}
\]

\[
= \sum_{i=1}^{n} t_i (PO_2/PO_2^{22})^{22} + t_{n+1} (PO_2/PO_2^{22})^{22}
\]

\[= \sum_{i=1}^{n+1} t_i (PO_2/PO_2^{22})^{22}
\]

\[= \sum_{i=1}^{n+1} t_i (PO_2/PO_2^{22})^{22}
\]
Thus
\[
\text{DMG}_{n+1} = a t_{n+1}^2 \left( \frac{PO_2_{n+1}}{PO_2} \right)^2
\]
\[
= a \sum_{i=1}^{n+1} t_i \left( \frac{PO_2}{PO_2_{n+1}} \right)^{1/2} \left( \frac{PO_2_{n+1}}{PO_2} \right)^2
\]
\[
= a \left( \sum_{i=1}^{n+1} t_i \frac{PO_2_{n+1}^2}{PO_2^2} \right)^2
\]
\[
= a \left( \sum_{i=1}^{n+1} t_i PO_2^2 \right)^2
\]

For \( PO_2 \) as a continuous function of \( t \), Eq. A2 yields
\[
\text{DMG}_t = a \left( \int_0^{t_{\text{ex}}} PO_2^2 \, dt \right)^2
\]

For all-or-none effects, DMG should be replaced by \( K \), and the parameter \( a \) should be omitted, giving
\[
K = \left( \sum_{i=1}^{n+1} t_i \right)^2
\]

or
\[
K = \left( \int_0^{t_{\text{ex}}} PO_2^2 \, dt \right)^2
\]

**APPENDIX B**

**Solution of the Parameters of the Power Equation**

The power equation describes the increasing risk of CNS oxygen toxicity as \( K \) approaches
\[
K = t^2 PO_2^2
\]

From the available data, in the \( i \)th individual exposed to \( PO_2 \), CNS oxygen toxicity occurs at time \( t_i \). There are individuals in whom toxicity does not occur, so that \( t_i \) may be censored. Formally, the observations are given in the following forms
\[
(y_i, \delta_i, PO_2), \quad i = 1, \ldots, n,
\]

where \( y_i = \min(t_i, c_i) \), \( \delta_i = I_{t_i \leq c_i} \), and \( c_i \) are the censor variables, and \( \delta_i \) is the indicator showing whether the observation is censored or not. The goal is to fit the censored data (Eq. B2) to the model (Eq. B1).

Considering \( t \) as the response variable, one can write
\[
\ln(t_i) = \frac{1}{2} \ln(K_i) + \frac{1}{2} c \times \ln(PO_2)
\]

Thus \( c \) and \( K \) can be estimated by using parametric regression techniques for the survival data. The idea is that
\[
Z_i = \frac{\ln(t_i) - (c/2) \ln(PO_2) - (\delta_i/2) \ln(K_i)}{\sigma}
\]

has some distribution \( f \), where \( \ln(t_i) \) can be censored. The likelihood function is written as follows
\[
1(c, K, \sigma) = \prod_{i \text{ uncensored}} f(Z_i) \prod_{i \text{ censored}} \int f(x) \, dx
\]

Then \( 1(c, K, \sigma) \) or \( \ln(1(c, K, \sigma)) \) is minimized over \( c, K, \) and \( \sigma \) numerically. Distributions for \( Z_i \) can be chosen from the following list: 1) Gaussian, \( Z_i \sim \mathcal{N}(0,1) \); 2) smallest extreme value, if \( t \) has the smallest extreme value distribution, then \( e \) has a Weibull distribution; and 3) logistic, yields a closed form expression.

In our computations, we used the smallest extreme value distribution. The results obtained are not so sensitive to the choice of \( f \) from the above list.

The risk can then be calculated from the normal distribution
\[
Z = \frac{\ln(t) - \mu}{\sigma}
\]

where \( t \) is in minutes, and \( PO_2 \) is in kPa.

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The opinions and assertions contained herein are the private ones of the authors and are not to be construed as official or as reflecting the views of the Israel Naval Medical Institute.

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