

THE HAZARD OF CENTRAL OXYGEN TOXICITY OCCURRENCE. THE RISK OF CENTRAL OXYGEN TOXICITY PART 4

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ABSTRACT

The modelling and analysis, of the risk of an occurrence of symptoms connected with central oxygen toxicity presented in this article, were based on survival analysis introduced with regard to the issues related to diving by Weathersby and Thalmann [1].

Key words: central oxygen toxicity, risk modelling.

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RISK MODELLING

The risk R of the occurrence of central oxygen toxicity CNSyn¹ will be understood in this paper as any other occupational hazard, that risk being: a possibility of divers losing their lives or suffering an injury to health in the course of oxygen exposures. The hazard F of the occurrence of CNSyn is a conditional probability related to the occurrence of risk R on condition of surpassing of a certain value of oxygen partial pressure $pO_2 > 100$ kPa. As it will be demonstrated, the oxygen partial pressure at the level of $pO_2 = 100$ kPa constitutes the agreed limit between a lack of symptoms² and the possibility of occurrence of CNSyn symptoms [2].

In concord with the previously discussed³ general biochemical theory of oxygen toxicity it is assumed that all types of toxic effects of oxygen on the human organism are caused by free radicals and oxygen metabolites. In the event of a lack of their deactivation by biochemical protective systems, such free radicals and oxygen metabolites may be potentially hazardous for particular elements of cellular structures. Modelling of the risk related to the emergence of harmful metabolites is sometimes referred to as the concept of Clark and Lambertsen [3].

With constant oxygen partial pressure $pO_2 = \text{idem}$ the emitted constant stream of a mass of non-deactivated harmful forms of oxygen $\dot{m}_1 = \text{idem}$ is reduced by a constant stream of a mass of removed oxygen metabolites $\dot{m}_2 = \text{idem}$, hence the alteration in the mass of harmful substances $\dot{m} = \frac{\partial m}{\partial t}$ in time t will be expressed with the following differential equation: $\frac{\partial m}{\partial t} = \dot{m}_1 - \dot{m}_2$. Assuming the limits of the mass $m \in [m_0; m]$ and time $t \in [0; \tau]$, the differential equation will be expressed as an integral: $\int_{m_0}^m dm = (\dot{m}_1 - \dot{m}_2) \int_0^\tau dt$. After providing a solution to the integral equation we will be able to obtain a mathematical model for the calculation of the mass of harmful oxygen metabolites accumulated in tissues m in the function of time $t = \tau$: $m(t = \tau) = m_0 + (\dot{m}_1 - \dot{m}_2) \cdot \tau$.

In normobaric conditions no toxic effect of oxygen is noted in healthy divers, hence it is possible to assume that the initial content of harmful oxygen metabolites m_0 as an innocuous inherent content or, by moving the scale, assume that its value is equal to zero⁴. When it is established that the constant stream of a mass $\dot{m}_1 = \text{idem}$ of non-deactivated harmful forms of oxygen is proportional to oxygen partial pressure pO_2 , we will be able to write: $\dot{m}_1 = \dot{c}_1 \cdot pO_2$, where \dot{c}_1 stands for a unit⁵ stream of the produced oxygen metabolites. The stream of the mass \dot{m}_2 of the removed metabolites is also constant and amounts to $\dot{m}_2 = \text{idem} = \dot{c}_2$.

Thus, the mass of harmful oxygen metabolites accumulated in the tissues in the function of time $m(t)$ for the moment in time $t = \tau$ will be expressed as the function: $m(t = \tau) = m_0 + (\dot{c}_1 \cdot pO_2 - \dot{c}_2) \cdot \tau$, which, after the transformation, will be written as: $\frac{m - m_0}{\dot{c}_1} = (pO_2 - \frac{\dot{c}_2}{\dot{c}_1}) \cdot \tau$. In accordance with previous assumptions, the value of the parameter $\frac{\dot{c}_2}{\dot{c}_1}$ is constant $\frac{\dot{c}_2}{\dot{c}_1} = \text{idem}$ and serves as the threshold value of oxygen partial pressure p_g above which the mass m of accumulated harmful metabolites begins to grow beyond the limit of the safe value for masses of such metabolites m_0 accumulated in tissues: $\forall_{pO_2 > p_g = \frac{\dot{c}_2}{\dot{c}_1}} m > m_0 \mid \dot{c}_1, \dot{c}_2 = \text{idem}$.

When reviewing the primary functions applied in survival analysis we will conclude that it is sufficient to determine one of them in order to describe the others – tab. 1. The most common functions in survival analysis are the functions of survival $S(t)$ and hazard $h(t)$ ⁶. A reliable evaluation of specific functions in survival analysis is possible with a sample size greater than $N = 30$, otherwise the estimated results will be burdened with errors.

The function of risk $R(t)$ may represent the probability of an occurrence of CNSyn in the function of time t . By use of the relationship $\forall_{t \geq 0} S(t) = P(T > t) = 1 - F(t)$ and $\forall_{S(t) > 0} S(t) = \exp\left[-\int_0^t R(t) dt\right]$ it is possible to express the distribution function $F(t)$ of the probability of CNSyn in the function of time t with the value of the function of risk $R(t)$:

Tab. 1

Relationships between certain functions encountered in survival analysis.

$$S(t) = 1 - F(t) = \int_t^\infty L(t) dt$$

$$L(t) = -\frac{d}{dt} \cdot S(t)$$

$$R(t) \equiv h(t) = -\frac{d}{dt} \cdot \ln S(t)$$

$$H(t) = -\ln S(t) = \int_0^t R(t) \cdot dt \equiv \int_0^t h(t) \cdot dt$$

$$S(t) = \exp[-H(t)] = \exp\left[-\int_0^t h(t) \cdot dt\right]$$

F – cumulative distribution function	L – probability density
h – hazard function	R – risk function
H – integrated hazard function	S – survival function

$$\forall_{F(t)} F(t) \equiv 1 - S(t) = 1 - \exp\left[-\int_0^t R(t) \cdot dt\right] \quad (1)$$

where: $F(t)$ – the function of the risk of occurrence of *CNSyn* is equal to the distribution function of the time of survival $F(t)$; $S(t)$ – survival function; $R(t)$ – function of the risk of occurrence of *CNSyn*.

When applying survival analysis in mathematical modelling of the occurrence of *CNSyn* symptoms it is necessary to distinguish the concept of the function of risk $R(t)$ of occurrence of *CNSyn* and the level of the risk $\Lambda(t)$ of occurrence of *CNSyn*.

The integral $H(t) = \int_0^t R(t) \cdot dt$ of the function of risk $R(t)$ from the moment $t = 0$ until t defines the integral⁷ risk $H(t)$ of occurrence of *CNSyn* in the period of time $t \in [0; t]$, is identified in the safety theory as the measurement of the level of risk $\Lambda(c, t)$ ⁸. The value of the function of risk $R(t)$ from equation (1) also constitutes the function of establishing the scale of damage $R(c, t)$, determining the probability of damage with the size of at least c in a sufficiently small unit of time after the moment t ⁹, thus determining the value of the level of risk $\Lambda(t)$ of occurrence of *CNSyn*. The values of the parameters of the function of risk $R(c, t)$ may be determined by their adjustment to experimental data.

The hazard¹⁰ $F(t)$ of occurrence of *CNSyn* is identified with the completion of the function of survival $S(t)$ and, in concord with the relationships between the functions collectively presented in tab. 1, it constitutes the distribution function of the survival time $F(t)$: $F(t) = 1 - S(t)$.

The function of risk $R(p_{O_2}, t)$ related to an exposure to the oxygen partial pressure p_{O_2} in a unit of time t should be proportionate to the mass of accumulated harmful oxygen metabolites $R(p_{O_2}, t) \sim \frac{m - m_0}{c_1}$, hence: $R(p_{O_2}, t) \sim p_{O_2} - p_g$, where p_g – represents the limit of oxygen partial pressure, below which the occurrence of *CNSyn* is very unlikely. By expansion of the function of risk $R(p_{O_2}, t)$ in a series it is possible to write it down in a form simplified to a single factor of the polynomial¹¹ as:

$$R(p_{O_2}) = [a_2 \cdot (p_{O_2} - p_g)]^{a_1} \quad (2)$$

where: a_1 and a_2 are proportionality factors.

THE RISK AND HAZARD OF CNSYN

It is assumed that oxygen (O_2) exhibits no toxic effect on the central nervous system (*CNS*)¹² with its partial pressure p_{O_2} equal to or lower than $p_{O_2} \leq 0.1 \text{ MPa}$ ¹³ [4]. During dives beyond the saturation zone the oxygen partial pressures p_{O_2} often exceed the defined limit¹⁴.

In the 1970s, the *US Navy* introduced modifications in the standards concerned with oxygen exposures due to the risk of occurrence of *CNSyn* symptoms. The changes involved a reduction in the allowable partial pressures to $p_{O_2} \leq 0,20 \text{ MPa}$, a division into standard and extraordinary exposures, and a reduction in the allowable stay times for particular exposures. In the 1990s, the *US Navy* modified the allowable oxygen exposure times for *CCR – SCUBA*¹⁵

with the purpose of ensuring greater flexibility of diving operations [5]. In 1991 *NOAA*¹⁶ changed the regulations concerning the allowable oxygen partial pressures during nitrox exposures¹⁷ – *Nx* [6]. The amendment involved approval of longer stay times with the preservation of allowable oxygen partial pressures in *Nx*, as well as setting maximum exposure time within a 24-hour period.

In deep dives, breathing resistance increases due to an increased density of the breathing mix. This may be accompanied with an increased accumulation of CO_2 in a diver's organism. With a diver's increasing distancing from the surface, the possibility of providing assistance or self-rescuing by divers becomes complicated, which enhances the risk of oxygen toxicity. Hence, the maximum permitted oxygen partial pressures in deep dives should be reduced¹⁸.

Similarly, during cave or wreck diving, due to a limited access to the surface, the same principles as those related to deep dives should be applied. The division into standard and extraordinary oxygen exposures is connected with the conditions of diving. Extraordinary exposures may be applied only with the purpose of rescuing human life or under other important circumstances [6].

An analysis of exposures with regard to the hazard of central oxygen toxicity was performed on the basis of a theory prepared in the 1980s with the use of survival analysis [7,8,9].

The defined allowable exposure times during tests on the safety of oxygen dives may be too conservative¹⁹ in relation to dives carried out with the use of breathing mixes²⁰, which is an important disadvantage. However, the thus conducted estimation is characterised by a clearly defined calculation of the hazard of central oxygen toxicity *CNSyn*.

One of the proposed algebraic models of the function of hazard $h(p_{O_2}) \equiv R(p_{O_2})$ in the anticipation of the threat of *CNSyn* is the relationship²¹ [10]:

$$\forall_{p_{O_2} \geq p_g} R(p_{O_2}) = a_0 \cdot (p_{O_2} - p_g)^{a_1} \quad (3)$$

where: $R(p_{O_2})$ – the function of the risk of occurrence *CNSyn*, p_{O_2} – oxygen pressure, p_g – oxygen partial pressure limit, $a_0 \cdot a_1$ – constant.

is the previously derived (2) function of risk $R(p_{O_2})$ resulting from the biochemical theory of oxygen toxicity, providing a good approximation to experimental data [11].

The risk R of occurrence of *CNSyn* symptoms (2) does not constitute a function of time ($p_{O_2}) \neq f(t)$ ²². The function of risk $R(p_{O_2})$ from the relationship (2) is used to calculate the threat F of the occurrence of *CNSyn* symptoms [11]. When *CNSyn* causes an interruption in the exposure after the time T_1 elapses, the threat $F_1(t, p_{O_2}) = 1 - \exp[-\int_0^{T_1} R(p_{O_2}) dt]$ related to the occurrence of *CNSyn* symptoms is calculated according to the relationships compliant with the Wiener theorem²³:

$$\forall_{p_{O_2} \geq p_g} F_1(T_1, p_{O_2}) = 1 - \exp\left[-a_0 \cdot (p_{O_2} - p_g)^{a_1} \cdot T_1\right] \quad (4a)$$

In the case when the exposure is finished after a given time T_0 without presenting any *CNSyn* symptoms, the

hazard $F_0(T_1, p_{O_2}) = \exp[-\int_0^{T_0} R(p_{O_2}) dt]$ may be expressed as follows:

$$\forall p_{O_2} \geq p_g \quad F_0(T_0, p_{O_2}) = \exp[-a_0 \cdot (p_{O_2} - p_g)^{a_1} \cdot T_0] \quad (4b)$$

The estimated values of $a_0..a_2$ and p_g are related to oxygen partial pressure p_{O_2} which in relationships (4) are expressed as $[p_{O_2}] = ata$, similarly as the oxygen partial pressure limit p_g is expressed as $[p_g] = ata$.

The estimated a_0 value represents a scale factor whereas the partial pressure limit p_g is a threshold beyond which $p_{O_2} > p_g$ the function of risk $R(p_{O_2})$ begins to exceed zero $R > 0$. In the discussed algebraic

mathematical threat model F for the occurrence of *CNSyn* symptoms, the value of the partial pressure limit p_g is always higher than $p_g \geq 1 \text{ ata}$, since it is assumed that the *CNSyn* symptoms do not occur below the oxygen partial pressure of $p_{O_2} < 1 \text{ ata}$.

With the scale factor estimated at $a_1 = 0$ the risk $R(p_{O_2})$ of occurrence is invariable $R = const$ irrespective of the value of oxygen partial pressure p_{O_2} : $R \neq f(p_{O_2})$. With the factor estimated at $a_1 = 1$ the function of risk $R(p_{O_2})$ shows a linear increase together with an increase of oxygen partial pressure p_{O_2} . For the value $a_1 > 1$ the said increase is faster than linear.

Tab. 2

The allowable exposure times and oxygen partial pressures of N_x approved by NOAA [6] with regard to the threat F_1 of the possibility of occurrence of central oxygen toxicity.

Oxygen partial pressure [MPa]	Allowable exposure time [min]	Hazard F_1 [%]
0.20	30	3.91
0.19	45	4.10
0.18	60	3.68
0.17	75	2.93
0.16	120	2.79
0.16	45	1.05
0.15	150	1.89
0.15	120	1.51
0.14	180	1.07
0.14	150	0.89
0.13	240	0.54
0.13	180	0.40
0.12	210	0.12
0.11	240	0.01

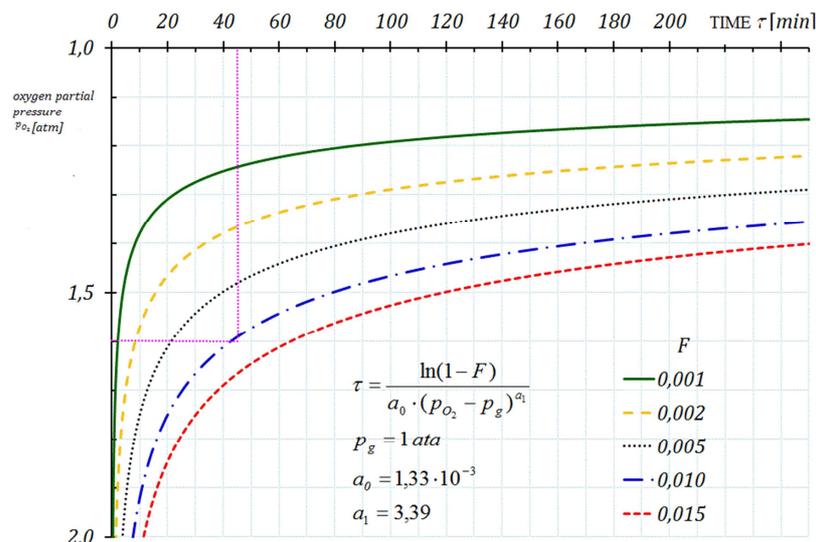


Fig. 1. Allowable oxygen partial pressures and exposure times in parametric relation to the threat F_1 according to (4a).

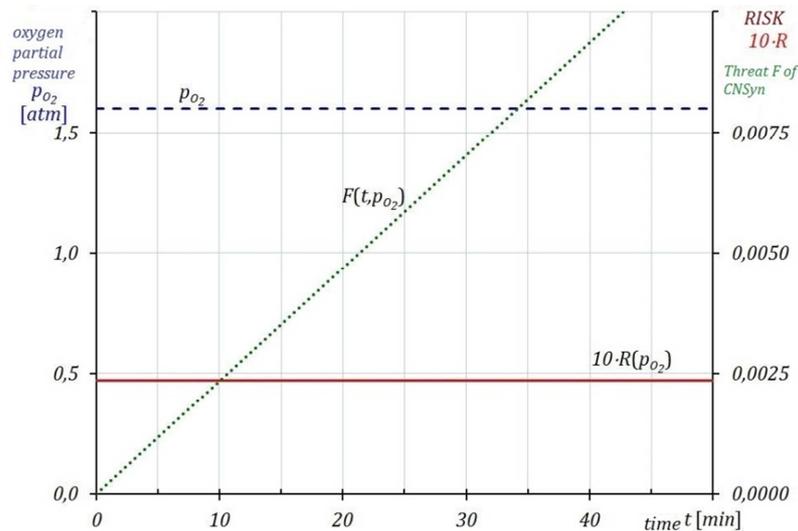


Fig. 2. The relation of risk R and the function of cumulative threat F_1 of occurrence of $CNSyn$ symptoms and time t according to a semi-empirical algebraic mathematical model (4a) regarding oxygen partial pressure $p_{O_2} = 160 \text{ kPa}$ [11].

Tab. 3

Allowable exposure times and oxygen partial pressures in dives with the risk of central oxygen toxicity at the level of $F_1 \leq 0.01$.

Oxygen partial pressure [MPa]	Allowable exposure time [min]
0.20	8
0.19	10
0.18	16
0.17	25
0.16	42
0.15	72
0.14	169

For the determined value of the oxygen partial pressure limit $p_g \equiv 1 \text{ ata}$ the parameter values of the algebraic mathematical model of the threat F of occurrence of $CNSyn$ estimated with the highest reliability method reached: $a_0 = (1.33 \pm 0.22) \cdot 10^{-3}$ and $a_1 = (3.39 \pm 0.5) - [11,12]$.

Most typically, planning of Nx exposures with regard to central oxygen toxicity is conducted on the basis of the tables of allowable oxygen exposures²⁵ Nx published in 1991 by *NOAA* ²⁶ [6]. An analysis of threat $F_1(T_1, p_{O_2})$ of $CNSyn$ occurrence in *NOAA*'s approach is presented in tab. 2. General estimations of the levels of threat $F_1(T_1, p_{O_2})$ of $CNSyn$ occurrence are depicted in fig. 1.

By comparing the oxygen exposures to the above survival analysis it is possible to evaluate the risk of central oxygen toxicity. If we assume that the allowable threat F_1 in dives performed with the use of Nx should be lower than or equal to the value of $F_1 \leq 0.01$, it will be possible to calculate the permitted exposure times according to the presented theory in the function of oxygen partial pressures – tab. 3.

OTHER METHODS OF CNSYN ESTIMATION

As already mentioned, the common planning of Nx exposures with regard to central oxygen toxicity is conducted on the basis of the tables of allowable oxygen

exposures Nx published in 1991 by *NOAA* [6]. However, these tables manifest an operational practice of many years rather than represent the results of scientific research [13].

In recreational dives it is assumed that the maximum allowed oxygen partial pressure p_{O_2} during the process of diving should not exceed $p_{O_2} \leq 143 \text{ kPa}$, whereas in the decompression phase – $p_{O_2} \leq 162 \text{ kPa}$ [13].

As an illustration, the *Abyss* software uses similar values to those proposed by *NOAA*, however it sharpens the requirements concerned with extraordinary exposures [14] – tab. 4.

It is common practice to apply the exponential model of threat elimination for $CNSyn$ during a rest at the surface, similarly as to medicine concentration. The time τ adopted in calculations is the time of partial threat elimination $CNSyn$ equal to $\tau = 90 \text{ min}$.

CONCLUSIONS

The survival analysis methods were introduced in diving-related issues by Weathersby and Thalmann [1]. The model of prediction of threat F of $CNSyn$ occurrence proposed by the *US Navy* and derived from this theory



Allowable exposure times and oxygen partial pressures in N_x as approved by *Abyss*²⁷ [14].

Standard exposures			
Oxygen partial pressure	Allowable exposure time	Limit used per each minute	Notes
[MPa]	[min]	[% · min ⁻¹]	
0.06	720	0.14	Typical exposures
0.07	570	0.17	
0.08	450	0.22	
0.09	360	0.28	
0.10	300	0.33	
0.11	240	0.42	
0.12	210	0.48	
0.13	180	0.55	
0.14	150	0.67	
0.15	120	0.83	
0.16	45	2.22	
Extraordinary exposures			
0.17	35	2.86	High risk <i>CNSyn</i>
0.18	25	4.00	
0.19	15	6.67	
0.20	10	10.00	Extreme exposures
0.21	5	20.00	
0.22	1	100.00	

seems to be precise enough. Its strength is the confirmation of the limit value of oxygen partial pressure $p_g \equiv 1 \text{ ata}$ observed by numerous researchers, following which the threat of *CNSyn* significantly increases. This allows to provide limits to a safe exposure time while breathing with a mix containing oxygen with a partial pressure above the limit value $p_{O_2} > p_g$.

In the proposed algebraic mathematical model the central toxicity dose in the process of diving only accumulates. Central toxicity dose is independent of the sequence in the diving phases²⁸.

It appears that despite the identical duration times of particular phases of the diving process, there should be a difference between a profile, which, for instance, begins the exposure with an excursion to a greater depth and the one with an excursion undertaken at the end of the diving process.

The Polish research on oxygen toxicity confirming the *US Navy* approach was not included in this article as they had been presented before [15]. This article presents merely the theoretical foundation constituting the grounds for the studies conducted in the Naval Academy of Gdynia and financed from educational

funds in the years 2009 – 2011 within a developmental research project No. O R00 0001 08 entitled: Designing decompression in combat missions.

The article is the last in the series of four papers devoted to the threat of central oxygen toxicity in hyperbaric technique.

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¹*CNSyn* Central Nervous Syndrome

²the actual occurrence of *CNSyn* symptoms below this value is possible, however extremely unlikely

³within this cycle of articles

⁴the value m_0 is an algebraic coefficient of scale shifting, hence adopting $m_0 = 0$ has no impact on the conducted considerations

⁵standardised stream per unit of oxygen partial pressure and a unit of time

⁶one of the important reasons for applying hazard function $h(t)$ lies in the fact that the conditional expected survival extension beyond the moment of time t_0 may be directly derived from it for $h(t > t_0)$

⁷complete

⁸formally speaking $\Lambda(c, t)$ constitutes the probability of occurrence of damage due to the realisation of a random variable $C(t)$, not smaller than c in the period t of the functioning of the system involving humans using technique while coping with the unique-surrounding environment [2]-

⁹the limits of the integration may also extend to encompass several hours after diving completion, however such a possibility is taken into account in modelling decompression sickness rather than oxygen toxicity

¹⁰hazard is understood as the conditional probability of the occurrence of *CNSyn* after the implementation of a particular hyperoxide exposure $p_{O_2} > 100 \text{ kPa}$

¹¹further factors of the expansion were omitted as it was found sufficient to rely on the accuracy to the first omitted factor

¹²*CNS* – Central Nervous System

¹³in *NOAA tables* this threshold was adopted as 0,06 MPa

¹⁴an additional complication lies in the fact that oxygen partial pressure may be subject to significant changes in the course of diving

¹⁵self-contained closed circuit re-breathers with oxygen as a breathing mix

¹⁶*National Oceanic and Atmospheric Administration*

¹⁷the changes were preceded with medical examinations conducted over the course of ten years, during the *Repex* programme [6] and dives with the use of nitrox mixtures as breathing gases

¹⁸in such operations there is a tendency to neglect the aspect of stress, which may significantly increase cerebral blood flow to a similar extent as the other previously enumerated factors

¹⁹the allowable exposures will be shorter than they could be in reality thus offering an excessive level of security for nitrox dives *Nx*; this effect will probably be absent in relation to heliox dives *Hx*

²⁰as it was already observed by Donald, adding nitrogen to oxygen enhances divers' tolerance to *CNSyn*. This was also confirmed with further tests conducted by the *USN* [13,16]

²¹an interrelation equivalent to the function of risk $R(p_{O_2}) \equiv h(p_{O_2})$ determining the probability of occurrence of *CNSyn* in a single-depth exposure procedure with the oxygen partial pressure p_{O_2} to which the diver is exposed and for the period of t

²²function of risk R describing the intensity of an occurrence of *CNSyn* in a given time is a constant value $R = \text{const}$ independent of time for any oxygen partial pressure p_{O_2} ; the effect of time on *CNSyn* is dependent on the moment of threat estimation $F(t, p_{O_2})$

²³ $S(t) = \exp[-H(t)] = \exp\left[-\int_0^t h(t) \cdot dt\right]$ – tab.1

²⁴the initially estimated value of the limit value of the partial pressure amounted to $p_g = (1,3 \pm 0,4) \text{ ata}$, however it was decided to adopt the value $p_g \equiv 1 \text{ ata}$ as more physiological [10]

²⁵the work was preceded with medical examinations conducted during the *Repex* programme [6] and during dives taking place over a period of ten years with the use of *Nx* mixtures as breathing gases

²⁶*National Oceanic and Atmospheric Administration*

²⁷it is possible to additionally gradually increase the oxygen conservatism by {10;25;50;75;99}%

²⁸the threat of *CNSyn* for profiles with an excursion to a greater depth does not depend on the time of its commencement