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ANALYSIS OF GASEOUS SUBSTANCE TOXICITY ASSESSMENT

Abstract: *Exposure to pollutants from the air indirectly affects the health risk level for the exposed population. This dependency is manifested through harmful health effects conditioned by the level of exposure and occurring after the interaction between the pollutant and the biological molecules-receptors in the human body. To fully grasp and assess health risk it is necessary to know the relationship and conditionality between toxic substance doses and the occurrence of unwanted biological and health effects. Consequently, this paper focuses on the application of adequate parameters in health risk assessment in the form of physical equations used to quantify the potential dose, the received dose, and the internal dose of pollutants from the air that are inhaled into the body. The paper also provides the assessment of substance toxicity as a function of exposure duration and dose.*

Key words: potential dose, received dose, internal dose, biologically effective dose, exposure, health risk.

INTRODUCTION

Toxicity assessment involves determining the chemical and physical effects of agents under certain conditions, which causes pathological changes and unwanted health effects in the exposed individual. Analysis of chemical agent toxicity assessment is performed by determining the quantitative value of the effect the chemical agent has per given uptake concentration – the dose and the occurrence of specific reactions in the exposed individual's body (the dose-response process). In addition to other purposes, this analysis can also be used to determine causality between individuals exposed to airborne pollutants and the occurrence of negative health effects per unit of air quality change.

Scientific study of the negative health effects of pollutants includes a broad spectrum of methods and procedures. In time, the methods used in the study of health effects have become more precise and will continue to evolve. Such progress is the result of improved available research and data processing techniques, as well as of the possibility that the future studies could be more focused on the key remaining issues, which were identified owing to the previous work in the field. The available studies of health effects that are potentially useful as the assessment basis are categorized as epidemiological studies, clinical studies, and animal experimentation studies.

DOSE-RESPONSERELATIONSHIP ASSESSMENT

The dose-response relationship assessment is a quantification of hazard in the identification stage of health risk assessment. It determines the relationship between different doses and the occurrence of unwanted health effects in humans (Figure 1). This relationship is determined by the use of experimental doses on animals and people, with the required prediction of unwanted effects for the people. An extrapolation with two variability categories is performed in the process:

1. Differences between animal species used in experimental studies and humans in terms of species variability and
2. Differences in sensitivity that can be expected among the humans in terms of certain individual subgroups (gender, age, health, etc.).

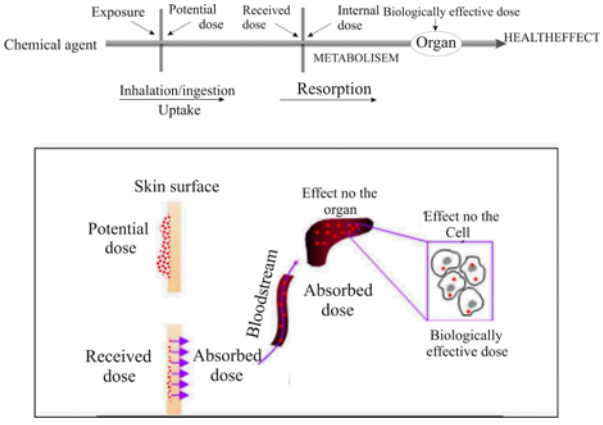

Figure 1. *Exposure-dose schematic*

It is difficult to determine with complete certainty the relationship between a received dose and the response it causes (response or internal dose) because there are certain absorption barriers inside the exposed individual's body that are inaccessible for direct determination of dose level (Figure 1).

POTENTIAL DOSE

Received doses can be calculated by approximation, but the focus is on the potential dose when determining the dose-response relationship. The potential dose is the quantity of the inhaled chemical agent inside the body whose effect considered as separate from the further effect of the agent in the body.

The general equation for potential dose calculation is:

$$D_{pot} = \int_{t_1}^{t_2} C(t) \cdot IR(t)\, dt \qquad (1)$$

where D_{pot} – potential dose [mg/kg/day], IR – respiratory rate per unit time [m^3/day], $C\,(t)$ – exposure agent concentration per unit time [m^3/kg/h], and t_1 – exposure duration [h].

Equation (1) can be explicitly expressed as the sum effect of chemical agent i, which results in known or expected reactions:

$$D_{pot} = \sum_i C_i \cdot IR_i \cdot ED_i \qquad (2)$$

If the exposure duration is short, concentration C_i and the respiratory rate per unit time IR_i can be taken as approximately constant values, in which case the following equation is used:

$$D_{pot} = \bar{C} \cdot \bar{IR} \cdot ED \qquad (3)$$

where ED – exposure sum duration for a specific response to the chemical agent effect, $\bar{C}$ and $\bar{IR}$ – arithmetic value of the C_i and IR_i. Equation (3) is not considered as valid in case of large oscillatory values of the C and IR parameters. In that case, the values of the aforementioned parameters in Eq. (2) are taken as approximate constants. If it is not possible to apply the equations (2) and (3), the potential dose is calculated with the basic form of Eq. (1).

To assess the risk, it is important to know the calculated doses that include the dose-response relationship. The dose-response relationship is often based on the potential dose. Nevertheless, there are other approaches in which the dose-response relationship is based on the internal dose. As previously stated, to determine health risk, it is necessary to know the toxicity of the affecting toxic agent. Unequivocally, chemical agent toxicity primarily depends on the dose intensity. Dose per unit time per unit body weight of the exposed individual is expressed as dose intensity. Dose intensity is not a constant quantity because absorption and resorption of a chemical agent can vary to a bigger or smaller extent in the exposed individuals. Equations (1), (2), and (3) provide the total exposure dose for an individual for a given exposure duration (Figure 2).

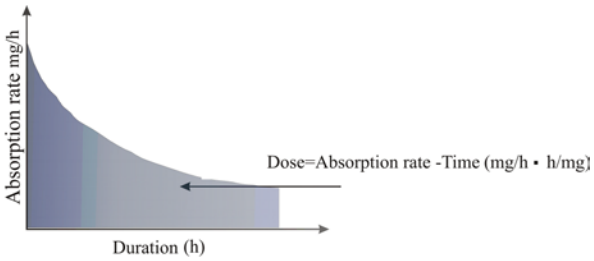

Figure 2. *Relationship between chemical agent absorption per individual body weight over exposure time – dose*

AVERAGE DAILY DOSE

Average Daily Dose (ADD) can be calculated starting with Eq. (1) and taking the average potential dose (average exposure time per individual body weight). Specifically, by using Eq. (3) derived from Eq. (1) and considering the dynamic balance of C and IR parameters, one can obtain the Average Daily Potential Dose (ADD_{pot}).

$$ADD_{pot} = \frac{\left[\bar{C} \cdot \bar{IR} \cdot ED\right]}{\left[BW \cdot AT\right]} \qquad (4)$$

where ADD_{pot} – average daily potential dose [mg/kg/day], BW – body weight of the individual [kg], AT – time expressed by days over the averaged exposure duration.

Arithmetic values of C and IR parameters in Eq. (4) are considered as approximate constants.

In case the exposed individual is afflicted with cancer, the average daily potential dose is calculated by substituting the AT parameter with the LT parameter in Eq. (4).

$$ADD_{pot} = \frac{\left[\bar{C} \cdot \bar{IR} \cdot ED\right]}{\left[BW \cdot LT\right]} \qquad (5)$$

where LT – probability of duration of life.

When assessing the unwanted effects of environmental (or, in this case, atmospheric) chemical agent exposure, it is also necessary to define the received dose. The entire dose inhaled into the body is not subject to tissue absorption. The dose that is absorbed, available for interaction with a biologically determined receptor and subject to further resorption is called the received dose. A portion of the received dose that penetrates the absorption barriers is subject to resorption and is known as the internal dose (Figure 1.). The internal dose influences the chemical agent reaction with a tissue cell and/or bodily fluids causing the actual health effect. A fraction of the internal dose that enables this reaction is called the biologically effective dose.

Internal dose

If we use the expression for potential dose calculation and substitute *IR* with the product of the absorption coefficient (K_p) and the specific barrier contact area (*SA*), we obtain the expression that defines the internal dose (D_{int}):

$$D_{\text{int}} = \int_{t_1}^{t_2} C(t) \cdot Kp \cdot SA(t)\ dt \qquad (6)$$

The rate of chemical agent transport through the barrier is not directly quantifiable, as it depends on several factors, such as the chemical nature of the agent; current physicochemical conditions of transport; chemical properties of the barrier; presence of other chemical agents with which the observed agent is mixed; etc. The relationship between the transport rate and the concentration of the chemical agent is commonly explicitly expressed as the absorption coefficient, which can be determined experimentally. The relationship between the concentration and the absorption coefficient is expressed by Fick's law:

$$J = Kp \cdot C \qquad (7)$$

where *J* – dynamic balance of the chemical agent's transport rate and its concentration in a given environment, *Kp* – absorption coefficient, which is determined experimentally for a given chemical agent and barrier and expressed as the chemical agent mass penetrating the barrier per unit time per unit barrier area [mg/s·cm^2], and *C* – internal dose, which is analogous to the potential dose as defined according to Eq. (3):

$$D_{\text{int}} = \bar{C} \cdot Kp \cdot \bar{SA} \cdot ED \qquad (8)$$

where $\bar{SA}$ – the magnitude of average exposure of a specific barrier area.

The internal dose can also be expressed analogously to Eq. (3) for the potential dose, by which the average daily internal dose can be obtained:

$$ADD_{\text{int}} = \frac{\left[\bar{C} \cdot Kp \cdot \bar{SA} \cdot ED\right]}{\left[BW \cdot LT\right]} \qquad (9)$$

To calculate the internal doses, it is important to establish a relationship between the potential, the received, and the internal dose. These doses are unidirectionally influenced, so the potential dose influences the received dose and the received dose influences the internal dose. Determination of this inter-relationship is possible only theoretically, based on the knowledge of toxicokinetics of a given chemical agent. The following equations can represent the relationship between the internal and the received dose:

$$D_{\text{int}} = D_{app} \int_{t_1}^{t_2} f(t)\, dt \qquad (10)$$

where: D_{app} – received dose, *f* [t] – complex non-linear absorption function expressed as the quotient of the chemical agent's absorbed mass and its received mass per unit time:

$$D_{\text{int}} = D_{app} \cdot AF \qquad (11)$$

where: *AF* – fraction of the absorbed chemical agent expressed as the quotient of the mass of the absorbed chemical agent (fraction mass) per received dose mass.

Combination of equations (1), (2), (3), (10), and (11) can yield the expression that defines the relationship between the doses:

$$D_{\text{int}} = D_{app} \cdot AF \cong D_{pot} \cdot AF = \bar{C} \cdot \bar{IR} \cdot ED \cdot AF$$

$$ADD_{\text{int}} \cong ADD_{pot} \cdot AF = \frac{\left[\bar{C} \cdot \bar{IR} \cdot ED \cdot AF\right]}{\left[BW \cdot AT\right]}$$

EXPOSURE ASSESSMENT AND HEALTH RISK ASSESSMENT

Exposure assessment, as a part of health risk assessment, begins after the chemical agent (pollutant), which is regarded as potentially causing unwanted health effects, has been identified.

Exposure assessment is performed by means of a qualitative-quantitative evaluation of the exposure magnitude and a determination of the exposure duration frequency and exposure effects manifestations. The magnitude of exposure is a function of the chemical agent exposure concentration and the time interval of its effect, and it is expressed with the following equation (Figure 3):

$$E = \int_{t_1}^{t_2} C(t)\, dt \qquad (12)$$

where: *E* – magnitude of exposure [mg/m^3/duration]; *C(t)* – concentration of agent as a function of time [mg/m^3]; and t_2 - t_1 – exposure duration [ED]. ED is a continuous period of exposure (e.g. a day, a week, a year, etc.).

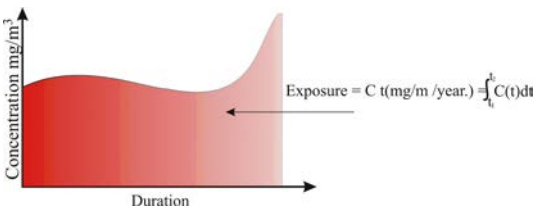

Figure 3. *Functional dependence of exposure on concentration and effect time*

Exposure concentration of the agent C(t) can be equal to zero during an interval of the exposure time. The total exposure is calculated for a given individual of a designated subgroup, for a specific chemical agent, and

for the corresponding exposure dose for the given period of time.

Exposure assessment is most often based on the reasonable maximum exposure (RME), which is defined as the maximum exposure present in the designated area. RME is assessed for each identified exposure pathway. In case the population becomes exposed to the same chemical agent through different exposure pathways, the RME has to reflect the actual impact of multiple exposure pathways.

Determination of general exposure conditions includes obtaining the general physical-spatial data on the location and the characteristics/habits of the potentially exposed population. General location data include, among other things, the data about the climate, vegetation, and surface and ground waters. The data on the potentially exposed population include the location of residential/occupational zones in relation to the pollution source location, as well as the habits and activities of the threatened population.

Identification of exposure pathways includes determining the ways in which the predefined population subgroups could be exposed to chemical agents. Each identified exposure pathway describes a unique mechanism by which the given subgroup could be exposed to chemical agents within or outside the pollution source location.

Exposure pathways are determined based on the types and locations of pollution sources, the manner of pollutant emission, physicochemical and chemical transformations of pollutants, as well as the living conditions of the observed subgroups in the exposed population.

Exposure quantification includes determination of the size, frequency, and duration of each identified exposure pathway. Exposure quantification is conducted by assessment of concentrations and calculation of toxic agent uptake.

Assessment of concentrations involves determination of concentrations of the identified chemical agents in an environmental medium, to which an individual of a given subgroup is exposed during a certain period of time. Concentration of chemical agents in a given environmental medium is established by use of standardized measuring methods; if measuring is not possible, the adequate mathematical models for concentration prediction can be used.

Uptake calculation involves calculation of the quantity of chemical agent coming into contact with the exposed person's body per unit body weight per unit time (expressed as mg/kg/day), according to the defined uptake pathway:

$$Uptak\ dose = C_{i,x}\left(\frac{IR_y}{BW_y}\right)\left(\frac{ED_i \cdot ET_i \cdot EF_i}{AT_x}\right)[mg/kg/day] \quad (13)$$

where: *Ci,x* – concentration of pollutant *x* in environment *i* [mg/m^3]; *IRy* – individual respiratory rate at rest per unit time for a representative individual in subgroup *y* in environment *i* [m^3/day]; *ETi* – exposure time of the representative individual in environment *i* [days/years]; *BWy* – body weight of the representative individual in the observed subgroup, represented as *y* [kg]; *EDi* – exposure duration for the representative individual in environment *i* [year]; and *ATx* – average time of effect duration of pollutant *x* [days].

Inhalation rate, distribution, and resorption of the inhaled air pollutant vary according to the features of individuals in a subgroup. Accordingly, the average uptake of air pollutants is assessed through parameters for a representative individual in a subgroup. Exposure in relation to average uptake of airborne pollutant *x* and in relation to the representative individual with average anatomical and physiological features in their subgroup, in environment *i*, is calculated with the following physical equation:

$$E_{i,x,y} = 0{,}001 \cdot C_{i,x}\left(\frac{IR_y}{BW_y}\right)\left(\frac{ED_i \cdot ET_i \cdot EF_i}{AT_x}\right) \quad (14)$$

where: *Ei,x,y* – exposure, or the average uptake of pollutant *x* as a function of time, for the representative individual *y* in the observed subgroup in environment *i* [mg/kg per day].

When assessing the respiratory rate, the following are to be considered: physical properties of the air (temperature, humidity, and pressure), as well as the physiological properties of the representative individual in the subgroup. Equation (14) implies total retention of the pollutant in the exposed individual's respiratory system. This takes into account the probability of harmful health effects due to exposure, and the value of risk in risk assessment includes all the receptors of the exposed individual.

In health risk assessment, exposure is implemented into the equation for the assessment of potential carcinogenic effects and the hazard quotient. The probability of potential carcinogenic effects is quantified with the following equation:

$$ICR_{i,x,y} = E_{i,x,y} \cdot SF_x \quad (15)$$

where: *ICRi,x,y* – probability of individual cancer risk for individual *y* exposed to pollutant *x* in environment *i*, *SFx* – carcinogenic coefficient of pollutant *x* [mg/kg/day].

The increased probability of health risk in individual *y* exposed to non-carcinogenic pollutant *x* in a given subgroup in environment *i* can be obtained by calculating the health risk hazard quotient (*HQ*):

$$HQ_{i,x,y} = \frac{E_{i,x,y}}{RfD} \quad (16)$$

where: $HQ_{i,x,y}$ – health risk hazard quotient for non-carcinogenic substances (dimensionless quantity).

CONCLUSION

Based on the data presented in the paper, the following conclusions can be drawn:

- In order to quantify the magnitude of health risk, it is necessary to determine the functional dependency of exposure and relevant dose. The relevant dose refers to the internal dose and the biologically effective dose, which are responsible for the harmful health effects. However, the relationship between the potential, the received, the internal, and the biologically effective dose is difficult to establish with complete certainty.

- In practice, exposure is regarded as the uptake dose and is accordingly determined by the adequate physical equation, which is implemented in the quantification of health risk through the determination of the hazard quotient and the probability of risk from carcinogenic diseases.

- Exposure implies contact of individuals (recipients) with pollutants (toxicants) and it is a function of pollutant concentration and their effect duration. If an individual is exposed to the air (exposure medium) of a given location, the concentration of pollutants in that location determines the level of exposure.

- In order to quantify the doses of toxic substances in the best possible manner, it is necessary to consider not only the pollutant properties, exposure duration, and the mean time of agent effects, but also the respiratory rate and the body weight of a representative individual.

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BIOGRAPHY

Amelija Đorđević was born in Niš. She graduated from the Faculty of Science and Mathematics in Niš, Department of Chemistry and received her magister and PhD (technical sciences – environmental protection) degrees from the Faculty of Occupational Safety in Niš. Professionally, she focuses on the problems of air pollution and environmental risk. She currently teaches eight courses at all academic levels at the Faculty of Occupational Safety in Niš. She published a university course book, two monographs of national importance, and over 60 scientific/professional papers in international and domestic environmental journals and proceedings. She participated in several scientific research projects financed by the government of the Republic of Serbia and the relevant ministries.

ANALIZA PROCENE TOKSIČNOG DEJSTVA GASOVITIH SUPSTANCI

Amelija Đorđević , Lidija Milošević, Marija Rašić

Rezime: *Ekspozicija ili izloženost zagađujućim supstancama iz vazduha indirektno utiče na stepen zdravstvenog rizika kod eksponirane populacije. Ova zavisnost se ostvaruje preko nepovoljnih zdravstvenih efekata koji su uslovljeni stepenom ekspozicije, a nastaju nakon interakcije zagađujuće supstance sa biološkim molekulima-receptorima u organizmu čoveka. Za potpuno razumevanje i procenu zdravstvenog rizika potrebno je poznavati odnos i uslovljenost doza toksične supstance na pojavu bioloških efekata i pojave neželjenih zdravstvenih efekata. Zbog toga je u radu dat poseban akcenat na primeni odgovarajućih parametara u proceni zdravstvenog rizika u vidu primene fizičkih jednačina koje se koriste za kvantifikovanje potencijalne doze, primljene doze i interne doze zagađujućih supstanci iz vazduha koje se unose inhalacijom u organizam. Takođe u radu je procenjena toksičnost supstanci koja je u funkciji dužine ekspozicije i doze.*

Ključne reči: potencijalna doza, primljena doza, interna doza, biološki efektivna doza, ekspozicija, zdravstveni rizik.