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Avaliação de Parâmetros Antioxidantes em Ratos Tratados com Sevoflurano *

Evaluation of Antioxidant Parameters in Rats Treated with Sevoflurane

Francisco J. L. Bezerra[1], Nilton Bezerra do Vale[2], Brunno de Oliveira Macedo[3], Adriana Augusto Rezende[4], Maria das Graças Almeida[4]

RESUMO
Bezerra FJL, Vale NB, Macedo BO, Rezende AA, Almeida MG – Avaliação de Parâmetros Antioxidantes em Ratos Tratados com Sevoflurano.

JUSTIFICATIVA E OBJETIVOS: *O sevoflurano é um éter halogenado com flúor que sofre biotransformação hepática através do citocromo P450 2E1. Éteres halogenados que sofrem biotransformação pelo P450 2E1 podem produzir espécies reativas do oxigênio (ERO) e promover enfraquecimento do sistema de defesa antioxidante. O objetivo deste trabalho foi investigar a relação entre a atividade das enzimas antioxidantes eritrocitárias e o sevoflurano.*

MÉTODO: *Os animais foram distribuídos em quatro grupos: Grupo 1 controle: apenas oxigênio a 100% (1 $L.min^{-1}$ por 60 minutos durante 5 dias consecutivos); Grupo 2 – sevoflurane 4,0% em oxigênio a 100% (1 $L.min^{-1}$ por 60 minutos durante 5 dias consecutivos); Grupo 3 – isoniazida (i.p.), 50 $mg.kg^{-1}$ de peso corporal /dia, durante 4 dias e em seguida tratados apenas com oxigênio a 100% (1 $L.min^{-1}$ por 60 minutos durante 5 dias consecutivos); Grupo 4 – isoniazida por via intraperitoneal na dose de 50 $mg.kg^{-1}$ de peso corporal, diariamente durante 4 dias, seguido da administração do sevoflurane a 4,0% em oxigênio a 100% (1 $L.min^{-1}$ por 60 minutos durante 5 dias). Após 12 horas da última exposição ao sevoflurane, os animais foram sacrificados e o sangue foi coletado através da veia porta para análise da atividade das enzimas antioxidantes.*

RESULTADOS: *Aumento da atividade específica da glicose-6-fosfato desidrogenase, diminuição da atividade específica da catalase, principalmente no grupo de animais pré-tratados com isoniazida e, em seguida, tratados com sevoflurano. A glutationa peroxidase não apresentou alteração na sua atividade.*

CONCLUSÕES: *A interação do sevoflurano com indutores enzimáticos do citocromo P450 2E1 pode propiciar a instalação do estresse oxidativo caso a exposição se torne prolongada e repetitiva.*

Unitermos*: ANESTÉSICOS, Volátil: sevoflurano; ANIMAIS: ratos; DROGAS, Antioxidantes: isoniazida; METABOLISMO: citocromo P-450 CYP2E1, glucosefosfato desidrogenase*

SUMMARY
Bezerra FJL, Vale NB, Macedo BO, Rezende AA, Almeida MG – Evaluation of Antioxidant Parameters in Rats Treated with Sevoflurane.

BACKGROUND AND OBJECTIVES: *Sevoflurane is a halogenated fluorinated ether that undergoes hepatic biotransformation through cytochrome P4502E1. Halogenated ethers undergoing biotransformation by P4502E1 can produce reactive oxygen species (ROS), weakening the antioxidant defense mechanism. The objective of this study was to investigate the relationship between the activity of erythrocyte antioxidant enzymes and sevoflurane.*

METHODS: *Animals were divided in four groups: Group 1 – control: 100% oxygen (1 $L.min^{-1}$ for 60 min during five consecutive days); Group 2 – 4.0% sevoflurane in 100% oxygen (1 $L.min^{-1}$ for 60 minutes during five consecutive days); Group 3 – isoniazid (i.p.), 50 $mg.kg^{-1}$/day for four consecutive days, followed by 100% oxygen (1 $L.min^{-1}$ for 60 minutes during four consecutive days); Group 4 – intraperitoneal isoniazid, 50 $mg.kg^{-1}$ daily for four days, followed by 4.0% sevoflurane in 100% oxygen (1 $L.min^{-1}$ for 60 minutes during five days). Twelve hours after the last exposure to sevoflurane, animals were sacrificed and their blood was collected through the portal vein for analysis of antioxidant enzymes.*

RESULTS: *An increase in the activity of glucose-6-phosphate dehydrogenase and a decrease in the activity of catalase were observed, especially in the group of animals pre-treated with isoniazid. Changes in the activity of glutathione peroxidase were not observed.*

CONCLUSIONS: *The interaction between sevoflurane and cytochrome P450 2E1 with enzymatic inducers can lead to oxidative stress with prolonged and repetitive exposure.*

Keywords: ANESTHETICS, Volatile: sevoflurane; ANIMALS: rats; DRUGS, Antioxidants: isoniazid; METABOLISM: cytochrome P-450 CYP2E1, glucose phosphate dehydrogenase

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1. Anestesiologista do Hospital Walfredo Gurgel; Mestre em Ciências Farmacêuticas
2. Anestesiologista da Maternidade Januário Cicco; Professor Doutor da Disciplina de Anestesiologia do Departamento de Cirurgia do Centro de Ciências da Saúde da UFRN
3. Mestrando do Programa de Pós-Graduação em Ciências Farmacêuticas da UFRN
4. Professor e Doutor do Departamento de Análises Clínicas da Faculdade de Farmácia da UFRN

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*Endereço para correspondência (**Correspondence to**):*
Dr. Nilton Bezerra do Vale
Rua Gen. Gustavo Cordeiro de Farias, S/N
Petrópolis
59010-180 Natal, RN
E-mail: niltondovale@hotmail.com

Evaluation of Antioxidant Parameters in Rats Treated with Sevoflurane

Francisco J. L. Bezerra, M.D.; Nilton Bezerra do Vale, TSA, M.D.; Brunno de Oliveira Macedo, M.D; Adriana Augusto Rezende , M.D; Maria das Graças Almeida, M.D;

INTRODUCTION

Sevoflurane ($CH_2F\text{-}OCH(CF_3)_2$ or flurometHyl 2,2,2-trifluoride-1 -[trifluomethyl] ethyl ether) is a halogenated inhalational anesthetic containing fluoride with low blood solubility, widely used for pediatric and outpatient anhesthesia[1]. It has a low extension (2-5%) hepatic biotransformation by the CPY2E1 isoform of the monoxigenase cytochrome P450 when compared to other halogenated agents: halothane (20%), enflurane (2%), isoflurane (0.2%), and desflurane (9%)[2]. Cytochrome isoenzymes constitute a family of hemeproteins found in the membrane of the endoplasmic reticulum of oxidative hepatocytes, being responsible for xenobiotic metabolism. The final metabolism of this halogenated compound results in the production of inorganic fluoride and the organic fluoride, hexafluoisopropanolol (HFIP)[3].

Reactive oxygen species (ROS) are produced during the use of oxygen by aerobic organisms. Those substances are capable of reacting with organic molecules (DNA, lipids, and carbohydrates) and are implicated in several pathological conditions, including atherosclerosis, cancer, and aging, as well as pathophysiological processes, such as inflammation, angiogenesis, and apoptosis[4-6]. Increased production of ROS is associated with changes in intracellular oxidative/antioxidative balance, which can have deleterious consequences for cell homeostasis. During evolution, cells created an antioxidant system that can convert ROS in inactive elements. Through the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione (GSH), magnesium and zinc ions, C and E vitamins, and the cofactor nicotinamide adenine diphosphate (NADPH), besides proteins such as albumin, ferritin, and ceruloplasmin, cells can eliminate ROS[7]. The enzyme CYP2E1, responsible for the hepatic biotransformation of sevoflurane, is capable of producing ROS like superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) during the catalytic cycle[8]. The presence of iron ions during this production of O_2 is capable of generating the highly reactive ROS hydroxyl radical (OH^-)[9]

Regarding the antioxidant effects of sevoflurane, some authors have suggested that this drug is capable of producing ROS, such as the hydroxyl radical (OH), anion peroxide (O_2^-)[10], and hydrogen peroxide (H_2O_2)[11], besides promoting lipoperoxidation[12], therefore weakening the antioxidant enzyme[13] system in several tissues. It has been speculated that sevoflurane is capable of changing the flow of electrons along the respiratory chain, at the mitochondrial level, promoting the formation of ROS[14].

On the other hand, recent publications have discussed the phenomenon of anesthetic preconditioning, in which short exposure to sevoflurane is capable of protecting the myocardium and other organs against the deleterious tissue effects promoted by the process of ischemia/reperfusion[15,16].

Considering the extremely reduced number of studies on the antioxidant defense mechanism after multiple exposures to sevoflurane, the objective of the present study was to evaluate the activity of antioxidant enzymes of erythrocytes in Wistar rats treated with sevoflurane, with or without enzymatic induction of CYP2E1 with isoniazid.

METHODS

Forty-two male Wistar rats with a mean weight of 280 g, and 90 days of age, maintained in cages with water and food *ad libitum*, and 12 h day/night cycles at the vivarium of the Health Sciences Center of the Universidade Federal do Rio Grande do Norte (UFRN), were used. This study was approved by the Animal Research Ethics Committee of the Health Sciences Center of UFRN. The animals were anesthetized in a 3200 cm^3 glass chamber using 100% oxygen, 1 $L.min^{-1}$. The anesthetic was released by a calibrated HB44 vaporizer (Abott, Madison, WI). After one hour of exposure, the rats received 100% oxygen (1 $L.min^{-1}$) until awakening, at which time they returned to their cages. Those animals were divided in four groups. Group 1, with nine animals (n= 9), received 100% oxygen at 1 $L.min^{-1}$ for 60 minutes during five consecutive days. Animals (n= 9) in Group 2 received 4% sevoflurane (1.8 $MAC.h^{-1}$) with 100% oxygen at 1 $L.min^{-1}$ for 60 minutes during five consecutive days. Group 3, with six animals (n= 6), received intraperitoneal isoniazid, 50 $mg.kg^{-1}$/d, for four consecutive days, followed by 100% oxygen at 1 $L.min^{-1}$ for 60 minutes for five consecutive days. Animals (n = 7) in Group 4 received intraperitoneal isoniazid, 50 $mg.kg^{-1}$/day for four days, followed by 4% sevoflurane in 100% oxygen at 1 $L.min^{-1}$ for 60 minutes during five consecutive days. Twelve hours after the last exposure, animals were sacrificed by cervical dislocation, and blood from the portal vein was collected, using heparin for anticoagulation.

The heparinized blood was centrifuged at a desk-top refrigerated centrifuge, model PK121R, ALC® ITALY (1000xg for 10 min at 4º C), and the plasma was separated. Erythrocytes were washed three times with NS and centrifuged at 1000xg for 10 minutes at 4° C. The precipitate was hemolyzed with °-mercaptoethanol 0.27 M pH 7.0. This hemolyzate was used to determine the activity of the enzymes glucose-6-phosphate dehydrogenase (G6PD)[17], catalase (CAT)[17], and glutathione peroxidase (GPx)[18].

Analysis of Variance was used for the statistical analysis of the results, followed by the Mann-Whitney U test, for intergroup comparisons.

RESULTS

The enzymatic activity of G6PD (Table I) showed a 5% increase in the sevoflurane group (G2). Group 4 had a significant increase when compared to G1 ($p \leq 0.01$) and to groups

Table I – Activity of Glucose-6-Phosphate Dehydrogenase in Rat Erythrocytes Treated with Sevoflurane and Pre-Treated, or not, with Isoniazid

Groups	Treatment	$mU.mg^{-1}$ of Hb
G1	Oxygen	17.27 ± 0.87 (n =9)
G2	Sevoflurane	18.24 ± 2.03 * (n = 9)
G3	Isoniazid	17.87 ± 0.62 * (n = 6)
G4	Isoniazid + sevoflurane	21.98 ± 1.26 ** (n = 7)

Results are expressed as mean ± standard deviation.
*Indicates statistically significant difference ($p \leq 0.05$) when compared to Group 4.
**Indicates statistically significant difference ($p \leq 0.01$) when compared to Group 1.

Table II – Catalase Activity in Rat Erythrocytes Treated with Sevoflurane and Pre-Treated, or not, with Isoniazid.

Groups	Treatment	$U.mg^{-1}$ of Hb
G1	Oxygen	371.41 ± 33.06 (n = 8)
G2	Sevoflurane	332.96 ± 47.28 (n = 10)
G3	Isoniazid	284.56 ± 16.21 * (n = 6)
G4	Isoniazid + sevoflurane	274.11 ± 14.10 ** (n = 11)

Results are expressed as mean ± standard deviation.
*Indicates statistically significant difference ($p \leq 0.05$) when compared to Group 1.
**Indicates statistically significant difference ($p \leq 0.01$) when compared to Group 1.

Table III – Glutathione Peroxidase Activity in Rat Erythrocyte Treated with Sevoflurane and Pre-Treated, or not, with Isoniazid

Groups	Treatment	$U.mg^{-1}$ of Hb
G1	Oxygen	0.88 ± 0.15 (n = 9)
G2	Sevoflurane	0.87 ± 0.21 (n = 9)
G3	Isoniazid	0.66 ± 0.13 (n = 6)
G4	Isoniazid + sevoflurane	0.64 ± 0.10 (n = 7)

Results are expressed as mean ± standard deviation.

G2 and G3 ($p \leq 0.05$). Results are presented in milliunits per milligram of hemoglobin ($mU. mg^{-1}$ of Hb).
A reduction in enzymatic activity of CAT (Table II), of approximately 10%, was seen in G2 when compared to G1. Animals treated with isoniazid followed by sevoflurane had a significant reduction ($p \leq 0.05$ and $p \leq 0.01$, respectively) when compared to G1. Results are expressed in units per milligram of HB ($U.mg^{-1}$ of Hb).
Significant changes in the enzymatic activity of glutathione peroxidase (GPx) were not observed in the treatment groups. Results are expressed as units per milligram of hemoglobin ($U.mg^{-1}$ of Hb).

DISCUSSION

Glucose-6-phosphate dehydrogenase is an enzyme that oxidizes glucose-6-phosphate to 6-phosphogluconolactone, in the pentose phosphate pathway, producing NADPH by reducing $NADP^+$ [19]. Isoniazid (INH) induces the hepatic CYP2E1 enzymatic system, which is responsible for the metabolism of some drugs, such as: acetaminophen, ethanol[20], isoflurane, and sevoflurane[21]. The increased enzymatic activity in animals treated with isoniazid and sevoflurane (G4) can be associated with INH-promoted enzymatic induction and possible oxidative damage secondary to this process. The isoenzyme CYP2E1 uses NADPH as electron donor during its catalytic cycle[20]. It is known that a reduction in NADPH levels or glutathione (GSH) oxidation is a strong activator of G6PD[17]. Thus, the enzymatic induction of CYP2E1 by INH depletes erythrocyte stores of NADPH, contributing for the increased activity of G6PD observed in G4.
Pre-treatment with isoniazid increases the defluorination rate of sevoflurane by 0.5-4 times, but this increase depends on the dose and duration of the pre-treatment, being effective after three days[22]. The mechanism of action of the enzymatic induction by isoniazid results, primarily, from the increase in the efficiency of messenger RNA translation. The amino group of the lateral chain hydrazide and the pyridine ring play an important role in the selective induction and magnitude of induction of the cytochrome isoform CYP2E1[25].
Besides enzymatic induction, the biotransformation of sevoflurane and INH, both associated with the production of inorganic fluoride, represents another factor possibly involved in the activation of G6PD in this group. Motta et al.[24] demonstrated an increase in the activity of G6PD in the submandibular glands of rats treated with sodium fluoride. Fluoride is also capable of stimulating the production of ROS (O_2^-) in polymorphonuclear leukocytes[25]. Therefore, consumption of NADPH, through the CYP2E1 catalytic pathway, and the fluoride, released during the biotransformation of sevoflurane, could have a synergistic effect, increasing the activity of G6PD observed in G4. Unlike our observations, an *in vitro* study demonstrated inhibition of G6PD by sevoflurane[26]. However, this study did not use animals or INH for enzymatic induction.
The isoform CYP2E1 is capable of producing ROS, such as O_2^- and H_2O_2, whose excessive amount in the body is capable of inhibiting CAT[27]. Consequently, the increase in ROS produced during the CYP2E1 catalytic pathway can be responsible for the inhibition of CAT activity observed in G3 (INH) and G4 (INH + sevoflurane).
Sevoflurane only promoted changes in the activity of CAT in the presence of the enzymatic inducer, and this result could be related with the higher concentration of fluoride, formed during the biotransformation of sevoflurane, and an increase in the activity of the CYP2E1 catalytic pathway. Fluoride is knowingly nephrotoxic in plasma concentrations above 50 μM and a potent metabolic inhibitor of several enzymes, including CAT[28]. Since it is an electronegative element, it can form complexes with metal cofactors like Cu^+, Zn^{++}, or Fe^{++}, present in the heme group of enzymes, such as CAT, as well as change the transcription of antioxidant enzymes[29]. A rise in fluoride could be responsible for most CAT inhibition.
The activity of glutathione peroxidase was not affected in the study groups. This enzyme is more sensitive to low concentrations of H_2O_2, and it is related with the activity of G6PD. Glutathione peroxidase depends on G6PD to receive the NADPH necessary for the reduction of its oxidized form. Those results are in agreement with those those found in the literature, such as

Yesilkaya et al, who investigated rabbit erythrocytes treated with two anesthetic agents, 1% halothane and 1.5% isoflurane, and did not observe significant changes in GPx activity in any of the study groups[30]. However, Durak et al. evaluated the activity of this enzyme in guinea pig hearts exposed to the same halothane treatment, and confirmed the reduction in the activity of GPx[31]. Therefore, the absence of changes in GPx activity observed in this study could be related to the behavior of this enzyme in different tissues, as well as the methodology used.

In a prior study, we observed an increase in the levels of thiobarbituric acid reactive substances (TBARS)[32], an indication of lipid peroxidation, in rats exposed to the same treatment. When we associated the results of that study to the ones observed in the present study, we observed the presence of lipid peroxidation, increased G6PD activity, and reduction in the activity of CAT. This profile indicates that, although the activity of G6PD increased, the other enzymes, CAT and GPx, were not capable to act against the increase in the production of ROS, probably promoted by the fluoride and the catalytic pathway of the enzyme CYP2E1.

In a study by Dikmen et al. [33] with rats treated with sevoflurane, the authors observed an increase in the activity of SOD, CAT, and GPx, but not TBARS. According to our study, this difference could be explained by the shorter treatment duration (five consecutive days in our study) and pre-treatment with INH.

We think this could be the profile observed in early sevoflurane exposure, i.e., an increase in the activity of antioxidant enzymes without lipid peroxidation, and, if this exposure is prolonged or repetitive, lipid peroxidation and a decrease in the enzymatic activity could develop, similar to the results of our study. Our results also favor the importance of fasting in the modulation the enzymatic activity of the mitochondria and endoplasmic reticulum on drug metabolism because rats (high metabolic rate) did not ingest anything for more than one hour during the five days in which sevoflurane was administered (groups G2 and G4), which also favors induction of CYP2E1.

Most studies have indicated a possible antioxidant effect of sevoflurane[15,16-34,35]; however, depending on the tissue, this could be beneficial or harmful. For example, the cardiac protection induced by myocardial ischemic preconditioning is a benefic effect of ROS produced by sevoflurane[16]. The production of ROS by sevoflurane would cause the activation of protein kinase C and the consequent opening of potassium channels sensitive to ATP, known as K_{ATP} (ATPase-dependent potassium channel), which have a beneficial effect during myocardial ischemia and reperfusion. Opening of those channels is related with a reduction in the mitochondrial concentration of calcium and greater efficiency in the myocardial use of oxygen during the enzymatic process of ischemia and reperfusion[35]. But the production of the superoxide anion secondary to the sevoflurane-induced endothelial dysfunction of segments of the aorta is an example of the harmful effects of ROS[36].

Note that the drugs used during anesthesia are not the only ones responsible for the imbalance of the antioxidant defense system. The presence of clinical pathologies[37], the clinical condition of the patient before arriving at the operating room, the surgical trauma itself[38,39], and fasting, mentioned earlier, are important factors in the promotion of this imbalance.

A particular clinical situation involving the use of sevoflurane should not be forgotten: the use of this halogenated compound in individuals with erythrocyte deficiency of G6PD[40]. Those patients do not have a satisfactory production of NADPH, an important erythrocyte cofactor because it helps, indirectly, the activation of GPx, which is responsible for the elimination of peroxide from red blood cells[41] and also very important for the activation of CAT[42]. Therefore, those individuals are more susceptible to episodes of hemolysis due to the low production of NADPH and, consequently, reduced protection against oxidative agents. The technical option for sevoflurane seems to be pertinent in patients with G6PD deficiency as long it is restricted to a single exposure[43]. In theory, the risk of hemolysis would be lower, since it promotes an increase in the activity of G6PD, leading to an increase in the production of NADPH.

Patients with tuberculosis, especially those on long-term treatment with CYP2E1 inducers, such as isoniazid, especially the groups known as slow acetylators, deserve special consideration. The association of INH, alcohol, tobacco (CYP2E1 inducers) and G6PD deficiency in inhalational anesthesia with sevoflurane can result in oxidative stress, which damages red blood cells, especially if this use is prolonged and repetitive. If the administration of sevoflurane in patients with genetic deficiency of G6PD is technically required, serial hematocrits, detection of hemoglobin in the urine, and the levels of lactate dehydrogenase and potassium (signs of extravasation of red blood cell contents) are recommended to help detect signs of hemolysis during the anesthetic-surgical procedure. Thus, the use of other anesthetic technique, “antioxidant” and safer, such as total intravenous anesthesia with propofol, would be better to prevent the development of hemolytic anemia[44].

Summarizing, the results of the present study contribute with laboratorial evidence that the use of sevoflurane, a halogenated anesthetic, in patients using xenobiotic CYP2E1 inducers, such as isoniazid, could favor the production of ROS and weaken, or even exceed, the capacity of the antioxidant defense system to eliminate them, especially if the anesthetic technique chosen is repetitive and/or prolonged.

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RESUMEN

Bezerra FJL, Vale NB, Macedo BO, Rezende AA, Almeida MG – Evaluación de Parámetros Antioxidantes en Ratones Tratados con Sevoflurano.

JUSTIFICATIVA Y OBJETIVOS: *El sevoflurano es un éter halogenado con flúor que sufre una biotransformación hepática a través del citocromo P450 2E1. Los éteres halogenados que sufren biotransformación por el P450 2E1, pueden generar especies reactivas del oxígeno (ERO) y promover el debilitamiento del sistema de defensa antioxidante. El objetivo de este trabajo fue investigar la relación entre la actividad de las enzimas antioxidantes eritrocitarias y el sevoflurano.*

MÉTODO: *Los animales fueron distribuidos en cuatro grupos: Grupo 1 control: apenas oxígeno a 100% (1 L.min^{-1} por 60 minutos durante 5 días consecutivos); Grupo 2 – sevoflurano 4,0% en oxígeno a 100% (1 L.min^{-1} por 60 minutos durante 5 días consecutivos); Grupo 3 – isoniazida (i.p.), 50 mg.kg^{-1} de peso corporal /día, durante 4 días y enseguida tratados apenas con oxígeno a 100% (1 L.min^{-1} por 60 minutos durante 5 días consecutivos); Grupo 4 – isoniazido por vía intraperitoneal en dosis de 50 mg.kg^{-1} de peso corporal, diariamente durante 4 días, seguido de la administración del sevoflurano a 4,0% en oxígeno a 100% (1 L.min^{-1} por 60 minutos durante 5 días). Después de 12 horas de la última exposición al sevoflurano, los animales se sacrificaron y la sangre se recolectó a través de la vena porta para el análisis de la actividad de las enzimas antioxidantes.*

RESULTADOS: *Aumento de la actividad específica de la glucosa-6-fosfato deshidrogenasa, reducción de la actividad específica de la catalasis, principalmente en el grupo de animales pretratados con isoniazida y enseguida, tratados con sevoflurano. El glutatión peroxidasa no presentó ninguna alteración en su actividad.*

CONCLUSIONES: *La interacción del sevoflurano con inductores enzimáticos del citocromo P450 2E1 puede propiciar la instalación del estrés oxidativo en el caso que la exposición se prolongue y sea repetitiva.*