EXPERIMENTAL JUSTIFICATION OF THE MAXIMUM POSSIBLE CONCENTRATION OF DICHLOROHEXAFLUOROBUTENE IN A WORKING AREA

Shkaeva IE, Dulov SA, Nikulina OS, Solnceva SA✉, Zemlyanoi AV

Research Institute of Hygiene, Occupational Pathology and Human Ecology of the Federal Medical Biological Agency, St. Petersburg, Russia

To date, there have been no exposure standards for air concentrations of 1,4-dichlorohexafluorobutene (DCHF) in the work areas. The study was aimed to assess the toxicity of DCHF and to evaluate health hazard in acute, subacute, and chronic experiments. It was found that the substance was highly hazardous, DL_{50} in mice after intragastric injection was 79.0 mg/kg, CL_{50} was 229.0 mg/m^3, and in rats these values were 86,0 mg/kg and 670,0 mg/m^3. In animals, DCHF had a moderate local irritative effect on animal skin and ocular mucous membranes, as well as the skin resorptive effect. The 18.2 mg/m^3 threshold limit concentration for a single inhalation exposure to DCHF was defined based on the changes in behavior responses and blood parameters. The 30-day subacute inhalation experiment revealed the pronounced cumulative effect of the substance. The 4-months chronic inhalation study showed that the exposure of experimental rats to 16.8 mg/m^3 concentration of DCHF resulted in impaired function of central nervous system and cardiac activity, altered hematologic, biochemical, acid-base, and blood gas values, as well as in morphological alterations in lungs, which persisted after the 30-day recovery period. The chronic exposure threshold defined for DCHF was 2.2 mg/m^3, and the defined no observable effect level was 0.24 mg/m^3. Based on the study results, the maximum permissible concentration of DCHF in the air of the working area of 0.2 mg/m^3 was confirmed and approved, the substance was assigned hazard class 2, vapor + aerosol + (specific protection of skin and eyes required). Gas chromatographic method using electron-capture detection for determination of DCHF mass air concentration in the work areas has been developed and approved.

Keywords: freon RL316, toxicity, hazard, exposure standard, air quality in the work areas

Author contribution: Shkaeva IE — study planning, literature analysis, data interpretation, rationale for setting the exposure standard, manuscript writing; Dulov SA — study planning, overall management; Nikulina OS, Solnceva SA — literature analysis, toxicological testing, data acquisition and analysis, manuscript writing; Zemlyanoi AV — research management, manuscript writing.

Compliance with ethical standards: laboratory animals were kept and fed in accordance with "Guidelines for Keeping Laboratory Animals in Vivariums of Research Institutes and Educational Institutions" (RD-APC 3.10.07.02-09 dated 15.12.2009), as well as with "Sanitary and Epidemiological Requirements for the Device, Equipment and Maintenance of Experimental Biological Clinics (Vivariums)" (SP 2.2.1.3218-14 dated 29.08.2014).

✉ Correspondence should be addressed: Svelana A. Solnceva
Kapitolovo, str. 93, r.p. Kuzmolovsky, Vsevolozhsky r., Leningradskaja obl., 188663; solnceva.74@inbox.ru

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ЭКСПЕРИМЕНТАЛЬНОЕ ОБОСНОВАНИЕ ПРЕДЕЛЬНО ДОПУСТИМОЙ КОНЦЕНТРАЦИИ ДИХЛОРГЕКСАФТОРБУТЕНА В ВОЗДУХЕ РАБОЧЕЙ ЗОНЫ

И. Е. Шкаева, С. А. Дулов, О. С. Никулина, С. А. Солнцева ✉, А. В. Земляной

Научно-исследовательский институт гигиены, профпатологии и экологии человека Федерального медико-биологического агентства, Санкт-Петербург, Россия

До настоящего времени отсутствовал гигиенический норматив содержания 1,4-дихлоргексафторбутена (ДХГФ) в воздухе рабочей зоны. Целью работы было провести оценку токсичности и опасности ДХГФ в острых, подострых и хроническом экспериментах. Установлено, что вещество высокоопасно, DL_{50} для мышей при внутрижелудочном введении — 79,0 мг/кг; CL_{50} — 229,0 мг/м^3, для крыс — 86,0 мг/кг и 670,0 мг/м^3. ДХГФ обладает умеренным местным раздражающим действием на кожу животных и слизистые оболочки глаз и кожно-резорбтивным эффектом. Порог однократного ингаляционного действия ДХГФ обоснован на уровне 18,2 мг/м^3 по изменению параметров поведенческих реакций и показателей состояния крови. В подостром 30-суточном ингаляционном эксперименте обнаружены выраженные кумулятивные свойства вещества. В хроническом четырехмесячном ингаляционном эксперименте воздействие ДХГФ в концентрации 16,8 мг/м^3 вызывало у подопытных крыс нарушение функционального состояния центральной нервной системы, сердечной деятельности, изменения гематологических, биохимических показателей, кислотно-основного состояния и газообмена крови, а также морфологические изменения в легких, которые сохранялись через 30 суток восстановительного периода. Порог хронического действия ДХГФ установлен на уровне 2,2 мг/м^3, недействующая концентрация — 0,24 мг/м^3. На основании полученных результатов в качестве предельно допустимой концентрации ДГХФ в воздухе рабочей зоны обоснована и утверждена величина 0,2 мг/м^3, 2-й класс опасности, пары + аэрозоль + (требуется специальная защита кожи и глаз). Для измерения массовой концентрации ДХГФ в воздухе рабочей зоны разработан и утвержден газохроматографический метод с электронно-захватным детектированием.

Ключевые слова: хладон RL316, токсичность, опасность, гигиенический норматив, воздух рабочей зоны

Вклад авторов: И. Е. Шкаева — планирование исследования, анализ литературы, интерпретация данных, обоснование норматива, подготовка рукописи; С. А. Дулов — планирование исследования, общее руководство; О. С. Никулина, С. А. Солнцева — анализ литературы, проведение токсикологических исследований, сбор и анализ данных, подготовка рукописи; А. В. Земляной — руководство проводимыми исследованиями, подготовка рукописи.

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✉ **Для корреспонденции:** Светлана Андреевна Солнцева
ст. Капитолово, корп. 93, г.п. Кузьмоловский, 188663, Всеволожский район, Ленинградская обл.; solnceva.74@inbox.ru

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The compound, referred to as 1,4-dichlorohexafluorobutene (DCHF), is intended to be used as solvent, refrigerant or reagent for synthesis of perfluorobutadiene. Among the fluorine-containing hydrocarbon compounds, which include DCHF, toxicity increases with introduction of the chlorine atom into the parent molecule, and due to presence of double bonds [1, 2].

Currently, the best-known structural isomer of DCHF is 2,3-dichloro-1,1,1,4,4,4-hexafluorobutene [3–7], which is classified as highly toxic hazardous substance [8–12]: it causes pulmonary edema, nervous system damage, produces hepatotoxic and nephrotoxic effects, and also penetrates intact skin, exerting a pronounced skin resorptive effect. The researchers attribute the toxic effects of DCHF to dehalogenation processes, and to formation of metabolites that disrupt metabolic pathways.

So far, there was extremely limited information about the DCHF toxicity, and the DCHF exposure standards for the air in the work areas and environmental objects (ambient air, water, soil) have not yet been developed [14, 15].

The study was aimed at experimental confirmation of maximum permissible air concentrations of DCHF in the work areas.

METHODS

According to its physical and chemical properties, 1,4-dichlorohexafluorobutene-2 (synonims: DCHF, freon RL316; chemical formula: $C_4Cl_2F_6$; № CAS 360-88-3) is a clear colorless liquid with weak characteristic odor, having the relative molecular mass of 232.94, boiling point of 63 ± 5 °C, and melting point of –75 °C [1–2].

The studies were performed in accordance with guidelines [3–5] in outbred animals (white rats and mice with initial body weight of 220–250 g and 20–25 g respectively), obtained from the nursery of laboratory animals “Rappolovo” (Leningrad Region). The delivered batches of animals had veterinary certificates specifying the animals’ age and average weight, and indicating the absence of systemic diseases and parasitic infestation.

The animals were taken to quarantine unit of the vivarium, where they had been monitored for two weeks. The animals were kept under standard housing conditions; they were given a standard diet, and had free access to water. During the quarantine, each animal underwent daily examinations (behavior, overall condition, morbidity and mortality were evaluated). Cages with animals were in separate rooms. Lighting conditions: 12 h — light, 12 h — dark; the ambient temperature was maintained within the range of 19–25 °C, the relative humidity was within the range of 50–70%. Temperature and humidity were recorded daily. For the study the animals were divided into homogeneous groups, 8–10 animals per group.

Toxicity of DCHF was assessed amidst single and repeated exposure. The risk of acute poisoning with DCHF was defined for ingestion and inhalation, as well as for skin contact. In order to assess the irritant and skin resorptive effects, DCHF was applied to the clipped backs of rats, and the tails of the mice were placed into test tubes with the substance at 2/3 of the height (the exposure time in mice was 2 h, and in rats it was 4 h).

The inhalation exposure of experimental animals to DCHF was provided both under static conditions with free evaporation of the substance at room temperature, and in the specialized dynamic sealed stainless steel chambers with a volume of 600 dm^3. The specified concentrations of the substance were obtained with the calculated doses introduced into the steam generator. The exposure time in a single exposure was 2 h in mice, and 4 h in rats.

Cumulative properties of the substance were assessed in a subchronic experiment: the experimental rats had been exposed to DCHF by inhalation for 30 days, 4 h per day (except weekends).

Furthermore, chronic intoxication with DCHF was maintained during 4 months (4 h per day, except weekends) followed by monitoring of experimental rats during the 30-day recovery period.

DCHF concentrations in the air within the exposure chambers were controlled by the specially developed gas chromatography method.

The overall condition of experimental animals was evaluated using a set of methods that made it possible to detect changes at multiple structural and functional levels. Integral, physiological, hematological, biochemical, and morphological indicators were used. Plasma levels of DCHF and metabolites in experimental rats were defined by gas chromatography-mass spectrometry, and high performance liquid chromatography coupled with high resolution mass-selective detection.

Statistical analysis was performed based on comparison of mean values of the experimental and control groups. Chi-squared (χ^2) and Fisher's exact tests were used for assessment of differences between discrete data. The differences were considered significant when $p < 0.05$. Statistical data processing was performed using the Prizm 5 software.

RESULTS

The study found that based on acute toxicity DCHF was a highly toxic substance: CL_{50} in mice was 229.0 ± 10.4 mg/m^3, and in rats it was 670 ± 32.0 mg/m^3; DL_{50} was 79.0 ± 11.1 mg/kg and 86.0 ± 16.0 mg/kg respectively. Clinical manifestations of acute DCHF poisoning were as follows: short-term hyperkinesia, reduced respiratory rate, coordination impairment, adynamia, tonic-clonic seizures. The experimental animals died mainly on day 1–3 of exposure to the substance. Animal autopsies showed the following: lungs – atelectases, foci of hemorrhage, alveolar edema, patchy emphysema and bronchopneumonia, hemorrhagic infarction; kidney and liver — fatty degeneration of parenchyma; after acute freon intoxication by inhalation, DCHF and metabolites (acetylcysteine adduct and methyl sulfide) were detected in animal blood plasma and urine.

It was found, that DCHF had a moderate local irritative effect on animal skin and ocular mucous membranes, together with the skin resorptive effect. The threshold limit concentration for a single inhalation exposure (Limac) to DCHF of 18.2 mg/m^3 was calculated based on changes in behavioral responses and acid-base balance of blood. The 30-day subacute inhalation experiment revealed the pronounced cumulative effect of DCHF.

For the purpose of studying the chronic intoxication manifestation and assessing the risk of long-term intake, the experimental animals had been exposed to DCHF by inhalation for 4 months, 4 h per day (except weekends). The following concentrations of DCHF were used: 16.8 ± 3.8; 2.2 ± 0.9, and 0.24 ± 0.09 mg/m^3.

Dynamic testing of the animals was performed throughout the chronic experiment and 30 days after the inhalation exposure to DCHF (recovery period).

Prolonged exposure of experimental rats to DCHF concentration of 16.8 mg/m^3 resulted in impaired CNS function, mainly in altered exploratory behaviors.

The significant increase in the vertical activity was observed in experimental rats after 14 days of the experiment (4.2 ± 1.3

in the experimental group, 1.5 ± 0.8 in the control group). The maximum changes (6.2 ± 1.2 in the experimental group, 1.8 ± 0.8 in the control group) were detected after 30 days of exposure to DCHF. The significantly increased value of the parameter persisted throughout the 2-months exposure to the substance concentration of 16.8 mg/m3. After 90 days of the experiment the vertical activity of the treated animals became close to values of the controls. However, by the end of 4-months exposure to DCHF, this indicator significantly increased by 253%.

Similar direction of changes was observed when studying the emotional behavior of experimental animals. The dynamic changes in grooming behavior were characterized by maximum increase of the indicator after 30 and 60 days of the experiment, 2.5 and 3 times compared to controls respectively, and the decrease to control level by day 90 of exposure to DCHF concentration of 16.8 mg/m^3. By the end of chronic experiment, the direction of changes in grooming behavior of experimental animals remained the same, however, it was less evident (increase by 80% compared to controls).

The 4-months inhalation exposure of experimental animals to the substance resulted in cardiac abnormalities. Based on electrocardiographic findings, the significant decrease in the P wave height ($p < 0.05$) indicative of atrial dysfunction was detected after 30 days of experiment. The decrease in the R wave height by 43.2% compared to controls after 30 days, and by 25.7% by the end of the experiment was indicative of suppressed ventricular bioelectric activity. However, after 90 days of experiment the R wave height was the same as in control animals.

The S wave height on ECG of experimental rats decreased by 41.9% compared to controls after 30 days, and by 24.5% by day 120 of exposure to DCHF concentration of 16.8 mg/m^3. Depression of P, R, S, and T waves, as well as the prolonged QT and ST intervals in experimental rats are indicative of the cardiac conduction disorder, which may result from myocardial hypoxia associated with chronic inhalation exposure to the substance. At the same time, it should be noted that there has been an improvement in ECG readings on days 60–90 of the experiment, which demonstrates the implementation of compensatory and adaptive processes, as well as the animal adaptation to substance exposure. However, by day 120 of exposure to DCHF concentration of 16.8 mg/m^3, cardiac depression was observed, which was indicative of possible compensatory processes disruption associated with prolonged exposure to this concentration of the substance.

There were no significant differences in heart rate and respiratory rate between the experimental rats and the controls.

After 30 and 60 days of exposure to the substance, the significant ($p < 0.05$) decrease in total hemoglobin and mean corpuscular hemoglobin was observed.

The changes in the leukocyte formula of experimental rats included the increase in the number of lymphocytes by 31.5% compared to controls after 30 days, and by 91.8% after 60 days of the experiment.

Analysis of the acid-base status in experimental animals showed that inhalation exposure to DCHF concentration of 16.8 mg/m^3 resulted in changes in bicarbonate buffer system in the form of the decrease in base excess of the extracellular fluid (BEecf) by 46.6% compared to control rats after 30 days of the experiment. The base excess of blood (Beb) in experimental rats of this group significantly decreased by 36.4% compared to controls on day 7, and by 40% after 30 days of the experiment.

At the same time, there was a significant decrease in standard bicarbonate value. With an increase in the DCHF exposure time up to 60 days, the trend towards an increase in base excess of the extracellular fluid (BEecf) by 23.5% compared to controls, and base excess of blood (Beb) by 28% was observed.

By the end of 4-months inhalation exposure to DCHF the acid-base status of experimental rats was the same as of controls. Since there were no significant changes in blood pH, the experimental data obtained were indicative of compensatory and adaptive processes activation associated with exposure to DCHF during the first 30 days of the chronic experiment.

When studying blood gas exchange in experimental animals during the 60-day exposure to DCHF, the decrease in oxygen saturation (SO_2) and partial pressure of oxygen (pO_2) was observed. After 60 days of the experiment, in experimental rats of the same group, there was a decrease in alveolar oxygen tension with simultaneous increase in partial pressure of carbon dioxide. The longer lasting inhalation exposure to DCHF concentration of 16.8 mg/m^3 resulted in no significant changes of blood gas exchange in experimental rats.

Biochemical analysis showed that prolonged exposure of experimental rats to DCHF concentration of 16.8 mg/m^3 resulted in serum lactate level decrease by 38.9% compared to controls after 60 days, and by 36.4% by the end of the experiment. Along with a decline in serum lactate level during the chronic experiment, the inhibition of serum lactate dehydrogenase activity was detected in experimental animals. Moreover, there was a significant (by 83%) increase in triglyceride levels upon initial exposure to DCHF.

The data obtained are indicative of potential disorders of carbohydrate and lipid metabolism in experimental rats due to prolonged inhalation exposure to DCHF concentration of 16.8 mg/m^3.

The significant increase in alanine aminotransferase activity by 119.3% after 60 days of experiment was observed during the same period of observation, which was indicative of impaired liver function, which was back to normal by the end of the experiment.

The decrease in serum albumin levels by 79.1% in experimental rats after 60 days of exposure to DCHF concentration of 16.8 mg/m^3 was observed.

According to literature [1, 2], the toxic effects of chlorobutenes are associated with dehalogenation processes, as well as with free radical formation and peroxidation. That is why the oxidant and antioxidant system status was assessed in experimental rats after 60 and 120 days of exposure to DCHF.

When performing the assessment of total antioxidant capacity (TAC), it was found, that there were no significant differences in serum hydrogen peroxide levels between the experimental animals and the controls. Blood concentration of reduced glutathione (one of the antioxidant system components) was defined in experimental rats in order to assess the total antioxidant capacity (TAC) and the total antioxidant activity.

The interest in studying the concentration of reduced glutathione is also related to bodily processes of conversion of fluorochloroalkenes by hydrolysis, and formation of glutathione conjugates. It was found that blood concentration of reduced glutathione in experimental rats upon the prolonged exposure to DCHF showed no significant changes during all periods of the study. No significant changes in TAC were revealed in experimental animals compared to controls.

Pathomorphological studies showed that by the end of chronic experiment the lung weight coefficients increased by 134.2%, and liver weight coefficients increased by 113.6% in experimental animals compared to controls.

Histological examination showed that the 4-months exposure to DCHF concentration of 16.8 mg/m3 damaged lung

parenchyma in experimental rats. Thickening of the interalveolar septa, plasma impregnation of the interalveolar septa, and hyperemia of alveolar walls were detected; accumulation of red blood cells in the alveolar lumens was observed.

Pathomorphological studies of heart, liver, kidney, spleen, and brain of experimental animals of all groups revealed no differences with the controls.

When assessing genotoxic effects of DCHF, the significant increase in the degree of damage to DNA in the bone marrow cells of experimental rats was observed.

The percentage of DNA in the tail of experimental animals was 4 times higher compared to controls (12.5 ± 3.03 in the group exposed to DCHF concentration of 16.8 mg/m^3 vs. 3.1 ± 0.6 in the control group).

The data obtained confirm genotoxic effects of DCHF concentration of 16.8 mg/m^3.

DISCUSSION

Thus, comprehensive studies showed that prolonged inhalation exposure of experimental rats to maximum DCHF concentrations of the tested ones (16.8 mg/m^3) affected the function of nervous system (increased exploratory activity and anxiety), cardiac function (decreased bioelectric activity of the myocardium, depression of the P, R, S, and T waves, and prolonged QT and ST intervals), and resulted in altered hematologic, biochemical, acid-base, and blood gas values, as well as in morphological alterations in lungs. Analysis of dynamic changes in the bodily processes of experimental animals when exposed to DCHF concentration of 16.8 mg/m^3 showed significant changes in most indicators during days 30–60 of the chronic experiment. Such direction of impairments could be due to temporal activation of adaptive responses, including the DCHF detoxification systems. This assumption is supported by the results of metabolite profiling in blood plasma of experimental animals. When assessing metabolites of the substance in blood plasma of experimental animals after the 4-months exposure to DCHF concentration of 16.8 mg/m^3, the following metabolites were detected: cysteine adduct, acetylcysteine adduct, methyl sulfide, thioketone and volatile metabolite of 1-chloro-1,1,2,3,3,4,4,4-octafluorobutane, as well as the unmetabolized form of DCHF. The data obtained are consistent with literary data [8, 9], according to which the compound fluorinated derivatives of hydrocarbons undergo metabolic transformation resulting in formation of a number of metabolites. The main DCHF transformation pathway is the formation of glutathione adducts with the further degradation of adducts to cysteine and acetylcysteine adducts. According to some sources [12], glutathione S-transferase activity resulting from action of xenobiotics can be increased by 2–6 times.

It is also assumed that DCHF could be a chemical activator of glutathione S-transferase biosynthesis. As a result, during the chronic experiment, activation of protective and adaptive responses of the body occurs by day 90 of exposure to freon.

However, nothing would prevent the protective response disruption resulting in more pronounced clinical manifestations of intoxication. It should be noted that after the 120-day inhalation exposure to the substance concentration of 16.8 mg/m3, not only the impaired function of nervous and cardiovascular systems was observed, but also the significant alterations in a number of hematological and biochemical indicators, morphological alteration in lungs, and the signs of the substance genotoxicity.

After the 30-day recovery period following the 4-months exposure to DCHF concentration of 16.8 mg/m^3, the changes, detected in experimental rats, persisted (reduced vertical activity, depression of R, S, T waves together with prolonged PQ interval on the ECG, and changes in certain biochemical parameters: reduced serum lactate level, and increased activity of lactate dehydrogenase).

The 4-months exposure to DCHF concentration of 2.2 mg/m3 resulted in similar, but less prominent alterations in a number of tests. Thus, when assessing behavioral responses, the increase in vertical activity by 153% and grooming by 33.3% compared to controls was observed after 30 days of the experiment. After 60 days of experimental animal exposure to DCHF, the decrease in peripheral blood hemoglobin level by 95.3% was detected. Upon further exposure to DCHF, up to the end of the 4-months experiment, the total hemoglobin levels in experiment animals were the same as in controls.

The substance concentration of 0.24 mg/m^3 resulted in no significant alterations of the studied parameters.

CONCLUSION

The data obtained in the course of the 4-months experiment show the adverse effects of 16.8 mg/m^3 DCHF concentration on the overall condition of the animals. Based in the extent and nature of the alterations detected, DCHF concentration of 16.8 mg/m^3 should be considered the effect concentration. DCHF concentration of 2.2 mg/m^3, which causes minimum alterations in experimental animals, is considered the threshold value for rats. DCHF concentration of 0.24 mg/m^3, which causes no significant alterations of the studied parameters, is considered the no observed effect concentration. The safety factor, calculated in accordance with the guidelines, is 12. The the maximum permissible concentration of DCHF in the air of the working area of 0.2 mg/m^3 has been confirmed and approved based on study results; the substance has been assigned hazard class 2, v + a (vapor + aerosol) + (specific protection of skin and eyes required).

References

1. Uzhdavin JeR. Toksikologija i gigiena vysokomolekuljarnyh soedinenij i himicheskogo syr'ja. M., 1966; s. 71–72. Russian.
2. Filov VA, redaktor. Vrednye himicheskie veshhestva. Uglevodorody, galogenproizvodnye uglevodorodov: spravochnik. L.: Himija, 1990; 732 s. Russian.
3. Lazarev NV, redaktor. Vrednye himicheskie veshhestva. Organicheskie veshhestva: spravochnik, T. 1. L.: Himija, 1976; 300 c. Russian.
4. Fluorocarbons in Lower Atmosphere. EOS Trans Amer Geophys Union. 1979; 60 (50): 1030.
5. RTECS(R) National Institute for Occupational Safety and Health. Canadian Centre for Occupational Health Safety, 2005. Aailable from: https://www.cdc.gov/niosh/index.htm.
6. Clayton JW. Toxicology of the fluoroalkenes. Review and research needs Environmental Health Perspectives. 1977; 21: 255–67.
7. Lock EA, Berndt WO. Studies on the Mechanism of Nephrotoxicity and Nephrocarcinogenicity of Halogenated Alkenes. CRC Critical Reviews in Toxicology. 1988; 19 (1): 23–42.
8. Truhaut R, Boudene C, Jouany J, Bouant A. Experimental study of the toxicity of a fluoroalkene derivative, the

hexafluorodichlorobutene (HFCB). Fluoride. 1972; 5 (1): 4–14.
9. Gizhlarjan MS, Darbinjan NA. Metabolicheskaja aktivacija hlorzameshhennyh nenasyshhennyh soedinenij. V sbornike: Tezisy dokladov 1-go Vses. s"ezda toksikologov, Rostov-na-Donu, 1986 g. Rostov-na-Donu, 1986; s. 293–4.
10. Dekant W, et al. Bacterial-lyase mediated cleavage and mutagenicity of cysteine conjugates derived from the nephrocarcinogenic alkenes trichloroethylene, tetrachloroethylene and hexachlorobutadiene. Chem-Biol Interact. 1986; 60: 31–45.
11. Anders MW, et al. Biosynthesis and biotransformation of glutathione S-conjugates to toxic metabolites. CRC Crit Rev Toxicol. 1988; 18: 311–41.
12. Hayes JD, Pulford DJ. The Glutathione S-Transferase Supergene Family: Regulation of GST* and the Contribution of the Isoenzymes to Cancer Chemoprotection and Drug Resistance Critical. Reviews in Biochemistry and Molecular Biology. 1995; 30 (6): 445–600.
13. Dreehen B, Westphal G. Mutagenicity of the glutathione and cysteine S-conjugates of the haloalkenes 1,1,2-trichloro-3,3,3-trifluoro-1-propene and trichlorofluoroethene in the Ames test in comparison with the tetrachloroethene-analogues. Mutation Research. 2003; 539: 157–66.
14. Predel'no dopustimye koncentracii (PDK) vrednyh veshhestv v vozduhe rabochej zony. Gigienicheskie normativy GN 2.2.5.1313 — 03. M.: RRPOHBV Minzdrava Rossii, 2003. Russian.
15. Predel'no dopustimye koncentracii (PDK) vrednyh veshhestv v atmosfernom vozduhe naselennyh mest. Gigienicheskie normativy GN 2.1.6.1338-03. M.: STK Ajaks, 2003. Russian.
16. Metodicheskie ukazanija po ustanovleniju orientirovochnyh bezopasnyh urovnej vozdejstvija v vozduhe rabochej zony. M., 1985. Russian.

Литература

1. Уждавин Э. Р. Токсикология и гигиена высокомолекулярных соединений и химического сырья. М., 1966; с. 71–72.
2. Филов В. А., редактор. Вредные химические вещества. Углеводороды, галогенпроизводные углеводородов: справочник. Л.: Химия, 1990; 732 с.
3. Лазарев Н. В., редактор. Вредные химические вещества. Органические вещества: справочник, Т. 1. Л.: Химия, 1976; 300 с.
4. Fluorocarbons in Lower Atmosphere. EOS Trans Amer Geophys Union. 1979; 60 (50): 1030.
5. RTECS(R) National Institute for Occupational Safety and Health. Canadian Centre for Occupational Health Safety, 2005. Aailable from: https://www.cdc.gov/niosh/index.htm.
6. Clayton JW. Toxicology of the fluoroalkenes. Review and research needs Environmental Health Perspectives. 1977; 21: 255–67.
7. Lock EA, Berndt WO. Studies on the Mechanism of Nephrotoxicity and Nephrocarcinogenicity of Halogenated Alkenes. CRC Critical Reviews in Toxicology. 1988; 19 (1): 23–42.
8. Truhaut R, Boudene C, Jouany J, Bouant A. Experimental study of the toxicity of a fluoroalkene derivative, the hexafluorodichlorobutene (HFCB). Fluoride. 1972; 5 (1): 4–14.
9. Гижларян М. С., Дарбинян Н. А. Метаболическая активация хлорзамещенных ненасыщенных соединений. В сборнике: Тезисы докладов 1-го Всес. съезда токсикологов, Ростов-на-Дону, 1986 г. Ростов-на-Дону, 1986; с. 293–4.
10. Dekant W, et al. Bacterial-lyase mediated cleavage and mutagenicity of cysteine conjugates derived from the nephrocarcinogenic alkenes trichloroethylene, tetrachloroethylene and hexachlorobutadiene. Chem-Biol Interact. 1986; 60: 31–45.
11. Anders MW, et al. Biosynthesis and biotransformation of glutathione S-conjugates to toxic metabolites. CRC Crit Rev Toxicol. 1988; 18: 311–41.
12. Hayes JD, Pulford DJ. The Glutathione S-Transferase Supergene Family: Regulation of GST* and the Contribution of the Isoenzymes to Cancer Chemoprotection and Drug Resistance Critical. Reviews in Biochemistry and Molecular Biology. 1995; 30 (6): 445–600.
13. Dreehen B, Westphal G. Mutagenicity of the glutathione and cysteine S-conjugates of the haloalkenes 1,1,2-trichloro-3,3,3-trifluoro-1-propene and trichlorofluoroethene in the Ames test in comparison with the tetrachloroethene-analogues. Mutation Research. 2003; 539: 157–66.
14. Предельно допустимые концентрации (ПДК) вредных веществ в воздухе рабочей зоны. Гигиенические нормативы ГН 2.2.5.1313 - 03. М.: РРПОХБВ Минздрава России, 2003.
15. Предельно допустимые концентрации (ПДК) вредных веществ в атмосферном воздухе населенных мест. Гигиенические нормативы ГН 2.1.6.1338-03. М.: СТК Аякс, 2003.
16. Методические указания по установлению ориентировочных безопасных уровней воздействия в воздухе рабочей зоны. М., 1985.