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Dimethyl phthalate

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Dimethyl phthalate

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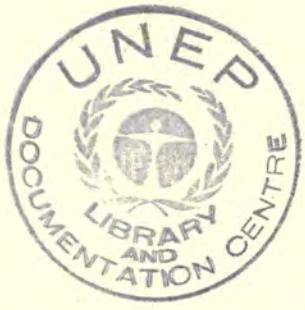

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The series is intended for toxicologists, higienists and all those responsible for evaluation and control of harmful effects of chemicals to human health and the environment.

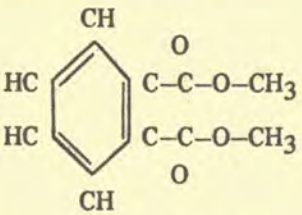
DIMETHYL PHTHALATE

Dimethyl phthalate (methyl ester of o-phthalic acid) is a complex ester of methyl alcohol and orthophthalic acid. It is a colourless, transparent homogenous oily liquid without mechanical impurities, with a weak specific odour [1].

Molecular formula – $C_6H_4(COOCH_3)_2$

Molecular weight: 194.19 [1, 2]

Structural formula:



Synonyms: Dimethyl ester of phthalic acid, dimethyl ester of benzol-o-dicarbonic acid, mollan M, palatinol M, solveol, fermine [2].

Melting point – 5.5°C [3]

Flammable limits – 145°C [3]
149°C [4]
146°C [4]

Density: at 20°C – 1.189 g/cm^3 [1, 2, 5]
1.190 g/cm^3 [5]
1.185 g/cm^3 [7]
at 25°C – 1.190 g/cm^3 [4]

Boiling point: under 760 mm of Hg – 282°C [1, 2, 4, 8]
– 283°C [5]
boiling limits under 20 mm of Hg – 160–164°C [3]

Pressure of saturated vapours: $2.69 \cdot 10^{-3}$ (at 20°C) [9]
13 mm of Hg (at 150°C) [5]
12.5 mm of Hg (at 150°C) [4]
76 mm of Hg (at 200°C) [1]

Water solubility: 0.45% (at 20°C) [2]
0.4% (at 25°C) [1]

Flash point: 157°C [1].

Refraction index: 1.5132–1.5134 (at 20°C) [1]
1.514 (at 20°C) [4]
1.5153 (at 20°C) [7]
1.514 (at 25°C) [3]

Viscosity: 11.4 centipoise (at 25°C) [1]
16.3 centipoise (at 20°C) [4].

Dimethyl phthalate is easily dissolved in alcohol, ester, acetone, chloroform and other organic solvents [7].

PRODUCTION

200 tons of pure dimethyl phthalate are produced to be utilized as repellents [10].

PRODUCTION PROCESS

Industrial production of plastifiers involves direct etherification of acids by alcohols, specifically phthalic anhydride by methanol. Production process of dimethyl phthalate cosists of several stages:

1. etherification,
2. neutralization and washing of the obtained ester,
3. distillation of excess alcohol,
4. treatment with sorbents and filtration of a ready product.

Etherification of carbonic acids and their anhydrides by alcohols (of orthophthalic acid by methyl alcohol in particular) is carried out in the presence of sour catalysts at 125–140°C with azeotropic distillation of the reaction water with alcohol in vacuum.

Sulfuric acid, benzosulfuric acid or toluene sulfonic acid are used as catalysts in most cases. Control over the procedure is conducted by the quantity of separated water and an acid number of the reaction mass which is usually equal to 2.5–3.0 at the end of etherification. The obtained raw ester is neutralized with water solution of caustic soda and washed with water. The alcohol which has failed to respond to the reaction and easily volatile products are distilled by a sharp vapour under vacuum. An ester obtained as the result of alcohol distillation is treated with sorbents (clarifying coal and bleaching clays) and filtrated [3, 11].

USE

Dimethyl phthalate is used as a plastifier for cellulose esters, especially for acetate cellulose; in a combination with other plastifiers, e.g. with triphenyl phosphate, diethyl phthalate and dibutyl phthalate, it plastifies polyvinyl acetate, rubbers and coumarone resins, mixes with polyacrylates and polymethylacrylates. It is also used for flotation of polymetallic ores [2, 11]. As a repellent primarily against two-winged bloodsucking insects, it has been widely used since 1929.

Dimethyl phthalate is considered to be a good repellent against Culicidae mosquitoes, Similiidae midges, Heleidae biting midges; its effectiveness is not high enough Tabanidae gad-flies, Stomoxys stable flies of Tabanida family, or Aphaniptera fleas [6, 7, 61, 62, 63, 64].

The content of dimethyl phthalate in different repellent preparations varies from 30 to 80% [11, 12, 13].

The most important index of a repellent efficiency appears to be the duration of its protective effect after its application to the human skin or fabric. This index vary according to the species, intensity of attack and physiologic condition of bloodsucking insects as well as a geographical locality. Thus, for example, in 1951 in the Astrakhan State Reserve dimethyl phthalate was found to repell mosquitoes for 240 minutes, but for only 62 minutes in 1952 [55], while in the sounthern districts of Turkmenia and Tadjikistan, dimethyl phthalate was effective there against mosquitoes for 150–180 min [65].

In Astrakhan region and Turkmenia the duration of protective effect of the some preparations was found to be lower twice or thrice compared to that in north-western regions of the USSR [66].

The repelling effect of 20–30% alcohol solution of dimethyl phthalate is 3–4 hours in a moderate climatic zone (Novgorod region) and about 3 hours in a much warmer steppe zone (delta of the Volga river). Its duration drops to 1,5–2 hours during sweating [67].

Meteorological factors are known to greatly influence the duration of dimethyl phthalate action. The preparation effect lasts the longest in a calm and dry weather. The duration of dimethyl phthalate mosquitoes repelling action is 3.2–5 hours, in dry weather, 4–5 hours against midges, and over 4 hours against biting midges (tests were conducted in the Polar regions) [52].

The duration of a repellent effect depends also on the preparation concentration. In conditions of northern regions of the USSR pure dimethyl phthalate repells mosquitoes for 5–6 hours, a 20% solution for 3.5–4 hours, a 15% solution for 2–3 hours, a 10% solution for up to 1.5 hour [6,50, 67]. Similar results have been obtained for midges [52]. Pure dimethyl and dibutyl phthalates and their 15% glycerin and paraffin jelly emulsions proved to be rather effective mosquitoe-repellents: the mean protection time of pure dimethyl phthalate is 6 hours, of a 15% emulsion on a paraffin jelly and glycerin – 5 hours, of a 25% alcohol solution – 1.5 hour [57].

The duration of a repellent effect also varies under different physical loads [68]. Thus, the duration of a dimethyl phthalate effect was found to be 2.0±0.5 hours (against mosquitoes) and 1.5±0.1 hour (against midges) in conditions of a light working load, but 0.5±0.2 hour, respectively, in conditions of hard working efforts.

Aerosol forms of dimethyl phthalate and some other repellents were found to be most effective and convinient for use. A jet of fine-dispersed spray from a container allows to apply the preparation economically on the skin or slothing in an even layer [69, 70].

To assess repellent action of the preparation it was suggested to calculate its minimum effective dose repelling 95% of bloodsucking insects. The mentioned index for mosquitoes is 3.5 g/m^2. This value was never determined for midges and biting midges, since dimethyl phthalate failed to repell 95 per cent of blood sucking insects with the consumption

rate even exceeding 40 g/m^2 (tests were conducted in the Komi Autonomous SSR) [71].

The repellent efficiency could be increased by finding a better preparation form and composition. For example, the preparation "Rebepin" (15% of benzoylpiperidine, 30% of dimethyl phthalate, 3 per cent of glycerin, 10 per cent of distilled water, 0.5 per cent of citral and 42.5 per cent of ethyl alcohol) is distinguished by its good dermofility and mild action. The duration of its protective effect equals 2.5–3 hours [10] due to a higher concentration of the active substance [72].

Glycerin and paraffin jelly emulsions of dimethyl phthalate proved to be more effective in comparison with solutions based on ethyl alcohol [61]. A single preparation application in the form of cream or a bar piece containing dimethyl phthalate provided protection against blood-sucking insects for 4–6 hours, while dubbing with technical dimethyl phthalate ensured insect-repelling action for 2–2.5 hours [73].

At present the Soviet industry manufactures such lotions as Taiga, Artek, Angara, aerosol preparations similar in action to Taiga, Taiga cream, etc., bars with dimethyl phthalate [74].

Sufficiently high repellent activity against midges has been revealed in trials of a number of solid preparations containing dimethyl phthalate. These preparations include 50% composition of benzoylperidine with dimethyl phthalate, 50% composition NIN-diethylamide of phenoxyacetic acid with dimethyl phthalate and so on. A longer protective action of solutions based on dimethyl phthalate has been proved compared to alcohol solutions of preparations: 10 hours and 3.5 hours accordingly [75].

One of the most successful compositions proves to be 58% solution of benzoylpiperidine in dimethyl phthalate with addition of 2% ethyl cellulose. Relative repellent activity of this preparation is twice as high as that of dimethyl phthalate [76].

Apart from the skin application of dimethyl phthalate tests were conducted when dimethyl phthalate was applied onto the fabric, viz. on protective nets, stockings, kerchiefs, collars and sleeves of shirts, T-shirts, tents, etc. [7, 51, 55]. When Pavlovsky nets are treated with cellulose jellies containing dimethyl phthalate, the protective effect preserves for up to theer months with daily use for 7–8 hours [7, 52].

To prolong the repellent effect of nets, it is recommended to dilute one weight part of cellulose in 10 weight parts of acetone and four parts of dimethyl phthalate [77].

After treatment of clothing without addition of acetyl cellulose, its protective properties preserve for 15–20 days [69]. The mosquitoes repellent efficiency of mosquito nets and curtains impregnated with dimethyl phthalate in the concentration of 20 ml/m^2 reached 89.4% (July-August), 60% (March) and 32% (August) [78]. It seems useful to saturate working clothes, underwear and socks with pure repellents by spraying or soaking them in emulsions based on repellents. In such cases the clothing aquires repellent properties against American dog ticks as well [66].

Dimethyl phthalate exerts a destructive action on caprone and nylon articles, it dilutes plastic materials, paints, varnishes, nickel and spoils all items made of them [51].

Tests of 63 ticks repelling synthetic compounds have shown that its repellent action index of dimethyl phthalate is 64, for diethyl phthalate it is 96, and 56 for dibutyl phthalate [63].

When used as an acarorepellent dimethyl phthalate has revealed a low activity, and by the index of repellentness and the intensity of ticks' attack it has been found to be close to the control (tests without a repellent) [79].

Midges and wood-louses are more sensitive to dimethyl phthalate than gnats; the duration of repellent effect of dimethyl phthalate used against these insects may last 6–7 hours [72].

A single application of dimethyl and dibutyl phthalates in the evening has been found to protect against mosquito stings up to the next morning in many cases; 2–3 g of the substance appear to be a sufficient dose to prevent stings in the face, neck and hands [61]. Owing to wrong storage of the preparation and its decomposition, the protective properties of dimethyl phthalate radically decline. Thus, after two years of storages the activity of the substance against midges and biting midges was found to drop from five to 2 to 3 hours [40].

A poor repellent effect of dimethyl phthalate and its several solutions has been revealed in relation to gad-flies, stable flies and fleas (human in particular) [7].

A certain repellent effect in relation of gad-flies is observed in the south (the Volga deltha), while in the north (Novgorod region) dimethyl phthalate fails to protect against gad-flies [6, 67].

The use of dimethyl phthalate against sandflies in foci of sandfly fever has resulted in a reduction of the disease rate by more than twice, compared to the incidence without the use of dimethyl phthalate [7, 61, 80]. However, dimethyl phthalate fails, to provide epidemic effectiveness in cases of leishmaniasis and sandfly fever since its repellent action is not long [81].

The working efficiency of some groups of workers was found to increase when dimethyl phthalate was used for repelling blood-sucking insects. For example, the application of dimethyl phthalate in case of loggers (solutions based ot alcohol and emulsions based on vaseline and glycerine) increased labour productivity on average by 20–30% [40, 60].

Control group of choppers was noted for having a considerable decline in output from 100–137% of the plan target to 83–96% in those days when loggers were treated with only its solution instead of dimethyl phthalate [72].

Treatment of large herds of reindeers (1000–2000 heads) with dimethyl phthalate diluted in water and added with an emulsifier (OP-7 or household soap) proved it to be a sufficiently effective repellent. Reindeers treated with 1% emulsion of dimethyl phthalate in the concentration of 100 ml per head were found to be satisfactory protected for about an hour. A treated herd without the use of protective measures spread over 0.5–1 hectare of pasture, while a treated herd – up to 5–10 and more hectares [56, 82, 83, 84].

A good repellent effect of dimethyl phthalate against midges and gnats has been shown on rabbits for 12 hours after which repeated treatment was necessary. This effect appeared to be higher against gnats

than against midges. It were cages where the animals were kept that were treated with the preparation but sometimes the rabbits fur was also treated [56].

PATHWAYS INTO THE ENVIRONMENT

Main sources polluting the environment are plants producing and utilizing dimethyl phthalate. The air pollution is also possible owing to the use of different household repellents.

Similar to other phthalates simultaneous migration of vapours and aerosols of dimethyl phthalate into the air may occur in conditions of production, especially when the technology involving heating is introduced [8].

CONCENTRATIONS

There is a large number of reports concerning the separation of esters of o-phthalic acid (dibutyl- and dioctyl phthalate) into various environments (air, water and media imitating food products). It is emphasized in these report that in view of its higher volatility, dibutil phthalate pollutes the air and other environments in considerably larger quantities than dioctyl phthalate [8]. One may assume that dimethyl phthalate as a more volatile products compared to dibutyl phthalate, will be easier separated from a polymer into the air and other environments. Mass-spectrometric and gas-chromatographic analysis of gas-isolations and water extracts from polyvinyl chloride materials identified alkylbenzols, saturated and non-saturated hydrocarbons, alcohols, ionole and dimethyl phthalate [14].

ENVIRONMENTAL FATE TESTS

One of the major characteristic features of dimethyl phthalate is its resistance to hydrolysis and influence of oxygen from the air [1]. One of the indirect indices of hydrolytic activity of the substance is the saponification number which for dimethyl phthalate is 571–583 mg/g [1] or 577.3 mg/g [3].

The saponification number (x) in mg/g of the substance is calculated according to the equation:

$$x = \frac{(v - v_1)\,28.05}{m},$$

where v – the volume of exactly 0.5 H of the hydrochloric acid solution used for titration in a control test, ml. v_1 – the volume of exactly 0.5 H of the hydrochloric acid solution used for titration of the tested solution, ml; 28.05 – mass of potassium hydroxide containing in one ml of exactly 0.5 H of the hydrochloric acid solution, mg; m – weight of a sample, in g.

The arithmetical mean of two and more parallel definitions approximated to a whole number is taken for the final result [1].

Kinetics of the dimethyl phthalate evaporation from four kinds of cotton fabrics gause, cambric, coarse calico and diagonal cloth which differ by the absorption capacity, were studies in laboratory conditions. Dimethyl phthalate was applied on fabric samples (50 cm^2) with the help of a calibration pipet. Prior to this, the maximum quantity of the repellent which can be absorbed and retained by every kind of the fabric were estimated, namely, for gause – 0.4 ml, for cambric – 0.3 ml, for coarse calico – 0.5 ml, and for diagonal – 1.5 ml. In this case the preparation was applied on the surface and distributed on the fabric most evently.

The mentioned samples were stored in a vertical position

a) at a temperature of 35–37°C (in thermostat)
b) at a room temperature of 18–20°C without forced ventilation.

The relative air humidity in this case was 52–55%.

The dimethyl phthalate volatility at 20°C is 28,57 mg/m^3, the evaporation rate is 9.22 (w relative).

The evaporation rate of dimethyl phthalate during first ten days was 3–4.6 mg from one cm^2 (under temperature 18–20°) and 4.2–4.6 mg from 1 cm^2 (at a temperature of 35–36°). In the following ten days these values were equal to 0.8–3.4 mg from 1 cm^2. On the 20-th day after the application of dimethyl phthalate on the fabric the preparation quantity on gause and cambric was 37–40%, on coarse calico and diagonal cloth it was 63–81% from the initial quantity.

The evaporation rate of dimethyl phthalate from different fabrics has been found to be directly related to the ambient temperature and the structural peculiarities of the fabric [9].

BIOCONCENTRATION / CLEARANCE TIME/MAMMALIAN METABOLITES

Applying 40% solution of dimethyl phthalate based on ethyl alcohol onto the skin of rabbits, the dimethyl phthalate concentration in the blood was determined by means of thin-layer chromatography in a non-fixed layer of alluminium. The skins area applied was 200 cm^2. The solution was applied once at the rate of 1.2 ml per one kg of the rabbit weight. During the experiment the presence of dimethyl phthalate in the blood was first detected 30 minutes after the application and averaged 18.4 mkg/ml, one hour later the concentration of dimethyl phthalate increased to 36.3 mkg/ml. For the next 8 hours the substance quantity was approximately on the same level (15–24 mkg/ml). In 24 and 48 hours the dimethyl phthalate concentration in the blood remained high enough (9–19 mkg/ml) [15].

Dimethyl phthalate in the form of 50% solution based on 96° ethanole was applied once and for a month in the dose 1500 mg/kg of the weight on the depiliated skin of the rats' back (about 30 cm^2). Detection of dimethyl phthalate and its metabolites (monomethyl phthalate and phthalic acid) were detected in the blood and in several organs (liver, kidneys, heart, spleen, lungs, brain, fatty tissue, skin). The substance and its metabolites were detected by a method of thin-layer chromatography on plates with a fixed layer of silica jel of the Silufor-UF-254 type.

After a single application dimethyl phthalate rapidly entered the blood and in 30 min its concentration achieved the maximum. In five hours

only traces of the product could be found in the blood of tested animals. Simultaneously with dimethyl phthalate quantities of monomethyl phthalate were found in the blood. Its concentration curve almost coincides with that of dimethyl phthalate in a few initial hours. At later stages the quantity of monomethyl phthalate appeared to be twice as high as that of dimethyl phthalate. Phthalic acid appears in the blood only in three hours and retains there for a short period of time.

Concentrations of dimethyl phthalate in 24-hour urine of rats were found to be smaller than that of phthalic acid by a factor of 10 and 100 times lower than that of monomethyl phthalate, i.e. 33.8; 256 and 396.7 mkg/ml, accordingly.

At repeated applications dimethyl phthalate is detected in most of the investigated organs 24 hours after the end of the exposure, comparatively rapidly disappearing from the lungs, heart and spleen, but retaining by the 10-th day only in the liver. Traces of dimethyl phthalate were detected in the blood, while none of them were found in the brain. Sufficiently large quantities of dimethyl phthalate were detected in the fatty tissue: 3294.0±0.356 mkg/g in five days and 808.1±352 mkg/g in 30 days.

In individual organs no dimethyl phthalate is found on the 3-rd and 5-th day (the blood, heart, spleen, lungs), in others it achives trace quantities by the 10-th day. Phthalic acid is found in considerable quantities in the kidneys, liver and heart where it remains practically for 10 days. No phthalic acid was found in the skin and fatty tissue [16].

There are indications proving that dimethyl phthalate decomposes into methyl alcohol derivatives of phthalic acid in the human organism [17].

Tests conducted on eight volunteers who had a third of their skin surface treated theer times with 50% solution of dimethyl phthalate, based on 96° ethanole, (the summary dose of 1250 mg/kg), showed a relatively slow accumulation of dimethyl phthalate concentrations in the blood. The maximum concentration of the substance was detected in six hours after the exposure stopped. By the end of the first 24 hours dimethyl phthalate was absent in the blood, but there were traces of monomethyl phthalate detected. Monomethyl phthalates, amounting to 200 mkg/ml, were found in the urine by the end of the first 24 hours, while dimethyl phthalate and phthalic acid were detected only as traces. Dimethyl phthalate and its metabolites in the human blood and urine were detected by means of thin-layer chromatography [16].

Repellents (Rebeftal lotion and cream) were applied onto the skin of thirty practically healthy volunteers, aged from 20 to 22, for one month. Some 5–7 ml of the lotion and 3–4 g of the cream were taken for one treatment; concentrations of dimethyl phthalate in preparations was 50 and 60%, accordingly. The presence of trace quantities of dimethyl phthalate was found in the blood (less than 0.002 mg/ml of blood) in two persons out of 15. No dimethyl phthalate was detected in the urine of these volunteers. Dimethyl phthalate in the urine and the blood was detected by the gas-chromatographic method [18].

A possibility of dimethyl phthalate entering the organism via cutaneous integuments has been shown both in experimental conditions and under practical observations. Dimethyl phthalate was found to distribute in almost all organs, retaining for a long time in the fat tissue. The rapid

disappearance of the substance from the blood and organs is associated with the substance's clearance with the urine and its intensive metabolism. The closed metabolites of dimethyl phthalate – monomethyl phthalate and phthalic acid – were identified.

MAMMALIAN TOXICITY ARRAY

Toxicity of dimethyl phthalate was studied in conditions of acute, sub-acute and chronic exposure under different pathway of the substance into the organism and on various species of laboratory animals. Vapours of phthalate plastifiers at an inhalation exposure cause no lethal poisoning under normal pressure and temperature [19]. No lethal concentrations were observed after heating dimethyl phthalate. The rated values of mean lethal concentrations for dimethyl phthalate were found to be 6760 mg/m^3.

Symptoms of poisoning appear under concentrations equal to 900 ÷ 1400 mg/m^3 (with the substance heating up to 90°) [20].

At the concentrations of dimethyl phthalate equal to 2 mg/l (in the shape of mist) cats revealed irritation of the mucous membranes, hypersalivation, mild excitation; at the concentration of 10 mg/l the mentioned symptoms become stronger [2].

The clinical picture of acute poisoning of laboratory animals with dimethyl phthalate was characterized by a brief period of irritation and excitation followed by development of inhibition, flaccidity, considerable loss in the body weight, adynamia [21].

The acute toxicity of dimethyl phthalate, containing 99.6% of active principle, was determined on mice and rats after its intragastric administration.

The mean lethal dose of the substance was found to be 6600 mg/kg (mice) and 7800 mg/kg (rats) [15].

After a single administration of dimethyl phthalate via the mouth, the mean lethal dose calculated by using a probit-analysis was 5.5±0.2 ml/kg for mice, 9.0±0.38 ml/kg for rats and 6.94±0.5 ml/kg (in a pure form and in oil solutions, accordingly) [2, 5].

There is a report indicating that LD_{50} of dimethyl phthalate when administered intragastrically to mice is 6.8 ml/kg [13], as well as 4300 (3644 ÷ 5074) mg/kg [25] and 6.8 (6.20 ÷ 7.38) g/kg [22, 23, 24].

LD_{50} for female mice is 8.2 g/kg (detected by the Van der Waerden method) [26, 27].

LD_{50} of the product for mice, rats and guinea-pigs was in the range of doses 4.8 ÷ 9.5 g/kg [21].

No differences in the species sensitivity to dimethyl phthalate on the level of lethal doses have been revealed [19, 20].

No distinct differences in sexual sensitivity in relation to dimethyl phthalate and other esters of phthalic acid have been revealed in mice and rats: LD_{50} for females and male mice after the intragastric administration of the substance were found to be 8.2 and 6.8 g/kg, accordingly [26].

The clinical picture of poisoning of mice after the intragastric administration of dimethyl phthalate was characterized by flaccidity (in 5÷10 min after the administration), respiration disturbance, cyanosis

of cutaneous integuments, rejection of food lasting for 1–2 days. In the survived animals symptoms of toxicosis were found to disappear gradually, but the animals hair remained fluffy [13].

Two-three hours after the preparation administration, the animals remained flaccid, taking the side position, their breathing would become rare and difficult. Reflexes (tactile and painful) remained, its twitching of the extremities and muzzle was observed. In 3–4 hours the animals died [5]. Death arrived against the background of the developed coma [20].

Pathomorphological investigation of the died animals revealed a sharply pronounced plethora of the internal organs and the brain, irritations of the mucous membranes of the stomach, moderate symptoms of albuminous dystrophy in the liver and kidneys [5, 20].

The threshold of acute inhalation effect of dimethyl phthalate was tested on rats in conditions of a 4-hour single exposure.

Changes in the nervous system, the peripheric blood, the respiration function, liver and kidneys have been chosen as intoxication indices.

The threshold concentration judging by the change in the respiration rate of rats is 50 mg/m^3, by the change in the summation-threshold index – 10 mg/m^3 [20, 21, 24].

The majority of researchers point out to the absence of a local irritative effect of dimethyl phthalate after its skin application. Single, repeated and sub-chronic (2-month) exposures of dimethyl phthalate to the skin of mice, guinea pigs and rabbits failed to reveal noticeable changes [13, 19, 20, 21].

After the application of 50% solutions of dimethyl phthalate in ethanole on the rabbits' skin (200 cm^2) at the ratio of 9 mg/cm^2 for 50 days, small-squamous desquamation was discovered on the skin, as well as the growth of a cutaneous fold from 2.15 to 2.4 cm in 30 days of the experiment and its decrease to 2.31 cm by the end of the experiment.

Hystological investigations of the skin revealed a slight enlargement of the epiderm due to the keratic layer. Moderate swelling and edema of collagenic fasciculus, at certain sites-swelling and proliferation of capillary endothelium were found in derma [15]

The data concerning the effect of dimethyl phthalate on the mucous membranes of the eyes, are controvertial. Introduction of two drops of dimethyl phthalate to the conjunctival eye sack of rabbits resulted in the development of conjuctivities, and in certain cases of keratoleukoma which recovered in 45–60 days [13].

The development of acute serous of seropurulent conjuctivitis without noticeable damage of the cornea was observed. The inflammation ceased in 48–72 h [15]. At the same time there are no indications to lesions of the mucosal membranes of the rabbits' eye after contact with dimethyl phthalate [21]. The resorptive effect of dimethyl phthalate was noted after its application on the skin.

LD_{50} of dimethyl phthalate after a single application on the skin is 38 (34.5 ÷ 41.42) g/kg [25].

It was also stated that the quantity of the substance entering the organism via the skin after a single application even in great doses caused no serious disturbances in the experimental animals [21].

Thus, weak toxicity of dimethyl phthalate is emphasized in the majority of researches conducted in USSR. According to the classification accepted in the USSR, dimethyl phthalate in conditions of an acute exposure is referred to slightly harmful compounds [22, 23, 28].

Evaluation of the cumulative properties of dimethyl phthalate was conducted by the method of Lim et al. under various initial fraction from the mean lethal dose (1/5, 1/10 and 1/20 of LD_{50}) after an intragastric administration. The cumulation factor of dimethyl phthalate estimated for 7,2 (at 1/5 of LD_{50}), 2,9 ÷ 3,2 (at 1/10 of LD_{50}) and 10 (under 1/20 of LD_{50}). The mentioned values I_{cum} of dimethyl phthalate, like those for other phthalates, attest to its moderate cumulative activity [24, 23, 28, 27, 29]. The absence of pronounced differences in coefficients of cumulation was observed in tests of different doses indicating the high hazard of chronic exposure to phthalates [19, 24, 28].

The total toxic effect of the substance after an intragastric administration in doses amounting to 1/10, 1/20 and 1/50 of LD_{50} revealed itself in lagging behind in the body weight increase, disturbances in the functional state of the liver, kidneys, nervous system, changes on the content of the peripheric blood, weight coefficients of the internal organs and their morphological structure [28].

Sharp plethora of internal organs was pathomorphologically marked alongside with moderate enlargement of interalveolar septa in the lungs, peeling off of the bronchial epithelium, focal turbid enlargement of hepatocytes in the liver, resuscitation of cells of the reticulo-endothelian system. More pronounced degree of albuminous dystrophy was found in the epithelium of convoluted tubules of the kidney where focal turbid enlargement achieved a degree close to necrobiosis.

Edema, chromatolysis and vacuolization were revealed in cytoplasma of the subcortial nodes and truncul regions of the brain; death of cells was also registered. Dystrophic alterations were registered in neurons of the anterior horns of the spinal cord (thoracal and lumbar regions). Dystrophy of the astrocytic glia has been found. Nervous fibres of anterolateral columns and peripheric nerves appeared to be demielinized; focal enlargements of axons were registered [24].

LD_{50} of dimethyl phthalate after a 90-day application on the skin is over 4 ml/kg [2], while after a single application LD_{50} exceeds 10 ml/kg.

After a 50-day skin application of the substance in the doses of 1250 mg/kg (rats) and 600 mg/kg (rabbits) and with the application thickness equal to 8–9 mg/cm^2, a reduction in the body weight of experimental animals was found. Rats were noted for having hyperglycemia and a tendency to a change in the ratio of albuminous fractions in the blood serum (growth in the quantity of α_2 and γ-globulins) and a verified increase in the weight of the liver.

Rabbits had the bilirubin concentration in the blood increased together with the quantity of α_1 and α_2-globulins. Sugar concentration in the blood was found not to change. There were no changes registered in the quantity of erythrocytes and leukocytes and in the leukocytic formula.

Hystologic investigations revealed granular and fatty dystrophy in the liver, circulatory and moderate dystrophic changes in the kidneys and myocardium, plethora in the brain.

A conclusion was made concerning a disturbance in the portein formating, carbohydrate and pigmentary function of the liver [15].

After a dimethyl phthalate application on the skin of male rats in the concentrations of 200, 1250 and 2000 mg/kg for three months, a verified change in the nervous system and the function of the kidneys was marked in testing the doses of 2000 and 1250 mg/kg [30].

Changes in the summation-threshold index and burrow reflex could be observed after a 19-day application of dimethyl phthalate on the skin of pregnant rats in the doses of 10000; 2000 and 200 mg/kg for four hours daily as well as after intraperitoneal administrations in the doses of 200 and 100 mg/kg [30].

White rats were subjected to 4-month exposure for four hours daily in the concentrations of 1.84 ± 0.03 mg/m^3 and 0.68 ± 0.08 mg/m^3.

Exposure to a larger concentration of dimethyl phthalate resulted in alteration of the body weight and the summation-threshold index two months after the beginning of the poisoning and in the recovery period; a drop in the hemoglobin content and a change in the quantity of erythrocytes in the blood one month after the inhalation started, hurried breathing following four months of the exposure. Besides, disturbances of diuresis (following months and in the recovery period), a change in the content of chlorides in the urine (following 40 days and in the recovery period), as well as an increase in the clearance of hippuric acid following with the urine beginning with the two months of the exposure were detected.

The smallest of the tested concentrations caused a verified change in the respiration rate (following one month after the beginning of the exposure). The mentioned changes were found to be in the range of physiologic fluctuations in the control.

A dimethyl phthalate concentration of 0.68 ± 0.8 mg/m^3 is considered as the one close to the threshold or to the non-effective in a chronic experiment.

The chronic effect zone of dimethyl phthalate was calculated according to the formula:

$$Z_{ch} = \frac{Lim_{ac}}{Lim_{ch}} = \frac{10 \text{ mg/m}^3}{0.7 \div 1.8} = 5.5 \div 14$$

The obtained value attests to a high hazard of dimethyl phthalate in conditions of a long-term exposure to small concentrations [20, 21, 24, 29, 31].

Inhalation exposure to the dimethyl phthalate for five hours during four months in the concentration of 2 mg/m^3 caused functional changes in the nervous system and liver of the animals as well as changes in the peripheric blood [2].

The data concerning the toxicity parameters of dimethyl phthalate are summarized in Table 1. The comparative assessment of toxicity of dimethyl phthalate and other phthalates (dimethyl-, diethyl-, dibutyl-, dinonyl- and didodecyl phthalates, dialkyl phthalates based on the mixture of alcohols $C_5 - C_6$, $C_7 - C_8 - C_9$, butylbenzyl phthalate, di (2 ethylhexyl) phthalate, di-3-(methylhexyl) phthalate, dicyclohexyl phthalate) has shown a progressive decline in the toxicity (up to 9 times) in the series from dimethyl phthalate to didodecyl phthalate, the 12-th member of the series. The turning point in toxicity occurs on the 8-th member of the series -- di-(2-ethylhexyl) phthalate [21, 32].

Thus the toxicity of phthalates diminishes with an increase in the number of hydrocarbons in the alcohol radical.

There have been several reports concerning acute poisonings of people swallowing dimethyl phthalate either in the pure form and in the form of lotions [2, 17, 53, 54]. The taken dose of various repellent preparations (Repudin, Angara, Taiga, Benphthalat) was as high as 150–200 ml. After swallowing Angara, Taiga, Benphthalat, dimethyl phthalate and diethyltolueneamide the patients recovered. Swallowing of other preparations resulted in lethal outcomes.

In the clinical picture of poisoning lesions of the central nervous system are most pronounced: inhibition, sopor, gradually aggravating till a complete loss of consiences, enlargement of pupils, muscular hypertonus, hyperreflexia, spasms, psychomotor excitation. The poisoning is coupled with pallor of the skin, pronounced acrocyanosis, tachycardia, arterial hypotension (up to collapse). Edema of the lungs is observed in the terminal stage of poisoning.

Hepatorenal defficiency is revealed on the 3-rd–4-th day after the poison taking. Palpation reveals painfulness in the epigastric region, enlargement and tenderness of the liver, a drop of sugar in the blood, increased bilirubin content, an increase of transaminase. The specific weight of the urine drops, the content of residual nitrogen and creatinine in the blood goes up, leukocytosis develops, the leukocytic formula shifts to the left, lymphopenia occurs.

Table 1

Some data of toxicity of dimethyl phthalate

Toxicity parameters	Values and character of changes	Animal spesies	Source
1	2	3	4
LD_{50}	not achieved	mice, rats	[19]
character of acute inhalation effect	6.760 mg/m^3 is a rated value. Symptoms of poisoning are exhibited at concentrations of	–	[21]
	900–1400 mg/m^3. Mucous membranes irritation, hypersalivation, light excitation under concentrations of 2.10 mg/l	mice, rats	[20]
		cats	[2]
LD_{50} (intragastric administration)	6,600 mg/kg	mice	[15]
	7,800 mg/kg	rats	[5]
	5.5±0.2 ml/kg	mice	[5]
	9.0±0.38 ml/kg (pure substance)	rats	[13]
	6.94±0.5 ml/kg (oily solution)	rats	[13]
	6.8 ml/kg	mice	[13]

Toxicity parameters	Values and character of changhs	Animal spesies	Source
1	2	3	4
	6.8 (6.2÷7.38) g/kg	male-mice	[26]
	8.2 g/kg	female mice	[21]
	4.8 g/kg	guinea pigs	[21]
	9.5 g/kg	rats	
	4.3 (3.644÷5.074) g/kg	mice	[25]
LD_{50} (skin application)	38 (34.5÷41.42) g/kg	rats	[25]
	10 ml/kg	–	[2]
Lim_{ac} a single, 4-hour inhalation	50 mg/m^3 (changed respiration rate)	rats	[20, 24]
	10 mg/m^3 (a change in the summation-threshold index		[21]
Local effect: Change of the skin (single exposure)	Practically absent (pure substance)	mice, rats	[21]
		guinea pigs	[13]
		rabbits	[20]
Chronic application	Fine-squamous scaling (50% solution in ethanole)	rabbits	[15]
Change in the mucous membranes of the eye	Practically absent;	rabbits	[21]
	serous, seropurulent conjuctivitis;	rabbits	[15]
	conjuctivitis, keratoleukoma of the cornea	rabbits	[13]
Local effect: Skin application (chronic exposure)	Changes of the nervous system and in the function of the kidneys were revealed after an application (3-month) in doses 1250 and 2000 mg/kg.	rats	[30]
	Functional-morphologic changes in a number of organs after a dose of 1250 mg/kg (50 days)	rats, rabbits	[15]
	Lethal effect after the dose over 4 ml/kg (90 days)		[2]

Toxicity parameters	Values and character of changhs	Animal spesies	Source
1	2	3	4
Cumulation factor	7.2 (administration of 1/5 LD_{50} by Lim et al. method 2.9÷3.2 (1/10 LD_{50}), administration by Lim et al method 10 (1/20 LD_{50}, administration by Lim et al. method)	rats	[24]
Chronic inhalation exposure	(4 months, for four hours daily). Concentrations of 1.84±0.03 mg/m^3 Changes in the body weight, the nervous system function, kidneys, respiration rate, morph. content of the peripheric blood	rats	[21]
Lim_{ch}	Concentrations of 0.68±0.08 mg/m^3		[21, 20]
Z_{ch}	14		[21, 24]
MAC	0.3 mg/m^3		[21]

The pathomorphologic picture after poisoning with dimethyl phthalate is composed of symptoms of rapidly arrived death: liquid state of the blood, plethora of the internal organs and multiple enormous hemorrhages in the serous membranes.

Final diagnosis "poisoning with dimethyl phthalate" is stated on the basis of results obtained after a chemico legal examination [17, 53].

The use of dimethyl phthalate and different related preparations as repellent means allowed to evaluate the general health of people who applied the repellents for a long time and determine their local effect.

Thirty practically healthy volunteers had their skin treated with Repeftal lotion and cream containing 50–60% of dimethyl phthalate, for one month. These volunteers had pulse rate, arterial pressure registered, the morphological blood content and the function of the kidneys and liver analyzed a day before the repellents were applied and then following 15 and 30 days after the beginning of the application. Daily check-ups of the skin and mucosal membranes of the oral cavity and the eyes were carried out. All tested persons failed to reveal visible changes (hyperemia, keroderma or hyperkeratosis) of the skin [18].

Following on application of undiluted dimethyl phthalate or its 10, 15 and 20% solutions in ethyl alcohol (with a cotton wad or by clean hand) on the open parts of the body (face, neck, hands) and in certain cases – on the entire upper part of the torso, only insignificant burning

of the eyelids was found in case an undiluted product was used. Alcohol solutions (up to 50%) fail to exert an irritating effect on the human skin and affect men's general state of health [56, 57].

No skin irritation was registered either after a long-term application of dimethyl phthalate (5–7 days for 4–5 hours daily). 27 wood-cutters out of 102 refused to apply dimethyl phthalate as a ticks repellent because they complained of headaches and eye irritation [49].

Many thousands of army servicemen used dimethyl phthalate for several months, but no cases of skin irritation or dermatitis were observed [6].

Dimethyl phthalate is not toxic even following its repeated application for 45 days in a row [55].

Application of dimethyl phthalate on a damaged skin (raw scraches after stings of gnats, etc.) caused rapidly disappearing irritation of the skin ceasing in 20–30 minutes. A case of dermatitis following a single application of the repellent on the crus and feet and their subsequent washing in an open water reservoir is described [58].

SPECIAL TOXICITY STUDIES

Carcinogenicity. No data on the carcinogenic effect of dimethyl phthalate is available.

Mutagenicity. No increase in the rate of chromosomal rearrangements have been revealed after 30 days of the dimethyl phthalate effect on the skin in the form of 20, 30 and 40% alcoholic solutions [30].

Male rats had applications of pure dimethyl phthalate on their skin in the doses of 200, 1250 and 2000 mg/kg during three months. After the end of the exposure they were mated with intact female rats which were slaughtered on the 19–20-th days of pregnancy. No disturbances in the fertilizing capacity of rats and changes of dominant lethal mutations in the sexual cells of males been found.

Furthermore, a cytogenetic analysis was conducted on the bone marrow (anaphase method) of male rats slaughtered after the end of 3-month application of dimethyl phthalate on their skin and of pregnant female rats killed on the 20-th day of pregnancy. No cytogenetic effect of dimethyl phthalate was revealed [30, 33].

A single intraperitoneal administration of dimethyl phthalate to mice in the dose of 1400 mg/kg (1/5 of LD_{50}) as well as a single and repeated (1 month) applications of the substance on the skin of rats in the form of 50% alcohol solution in the dose of 1250 mg/kg, did not entail any pronounced cytogenetic effect on the cells of the bone marrow.

The mutagenous effect was also absent after a single treatment of the skin with a dimethyl phthalate solution. Repeated applications of the substance revealed a distinct increase in the quantity of chromosome disorders in the hepatocytes of rats without changes in the spectrum of rearrangements [34].

Evaluation of the mutagenic properties of dimethyl phthalate was done by a method of dominant lethal mutations on C57 BL/6 male albino rats and tetrahybrid females. The substance was administered intraperitoneally in the dose of 1250 mg/kg (about 1/3 of the LD_{50}) in the form of a vegetable oil solution. The experiment lasted during the entire period

of spermagenesis (for five weeks continuously and on the 10-th week following the beginning of the test). Besides, white mice were applied dimethyl phthalate in the form of an alcohol solution in the dose of 1250 mg/kg (exceeding the recommended daily doses for humans calculated per one kg of the body weight by approximately 10 times) five times during two months.

The evaluation of the mutagenous effect was conducted by calculating the number of yellow bodies, implantation sites, alive and dead embryos. A mean number of implantations per a female, a mean number preimplantation losses per female and the mutagenity index (the ratio of dead implantations to the total number of implantation multiplied by 100) were also calculated. The statistical processing of the data was carried by the Krueger method; fertility of the males was estimated by the Wilcockson criterium.

As a result of the test no incidences of a higher frequency of dominant lethal mutations with sexual cells of C57B1/6 and non-pedigree mice have been revealed [35].

Neurotoxicity/Behaviour. Esters of o-phthalic acid possess selectivity of their effect on the nervous system. In determining the threshold of an acute single effect of these compounds, changes in the nervous system manifested themselves at concentrations which were lower than those causing disturbances in other investigated functions by a factor of 5÷8 [20, 22, 24].

In estimating the threshold of an acute effect of dimethyl phthalate (4-hour inhalation exposures of rats) changes in the peripheric blood, functions of the liver, the respiration rate and in other indices were detected at the concentration of 50–100 mg/m^3, but disturbances of the nervous system – at the concentration of 10 mg/m^3. The zone of a specific neurotoxic action (the ratio of the integral effect threshold to the acute specific effect threshold) for dimethyl phthalate is 5, indicating a high degree of its neurotoxicity [36].

Pathomorphologic investigations of the nervous system following the exposure to a number of phthalates, including dimethyl phthalate, revealed dystrophic changes in neurons of the anterior horns, demyelination of nervous fibres in the anterior-lateral columns of spinal marrow [29].

After using the behavioral reactions the selective effect of dimethyl phthalate and other esters of o-phthalic acid on the nervous system has been confirmed [32].

Potentiation. Local and resorptive actions of N,N-diethylamide of phenoxyacetic acid in the doses of 62.5 mg/kg and exceeding those by 15 times as well as their mixtures with alcohol and dimethyl phthalate were studied in experiments on rats and rabbits. Animals treated with ethanole and dimethyl formamide in the ratio 1:1 and by pure N,N-diethylamide of phenoxyacetic acid were used as the control. Such tests allowed to evaluate the effect of combinations of substances and their separate action. Exposure lasted for 50 days.

Smaller body weight was detected in all groups of animals including those which were exposed to dimethyl phthalate coupled with ethanole. The condition of the peripheric blood and main urine indices appeared to be unchanged in all groups of animals.

A decrease in the concentration of total protein in serum turned out to be more pronounced under combined action of N_1N-diethylamide of phenoxyacetic acid and dimethyl phthalate. The globulin quantity also grew due to -globulins. Concentrations of sugar in the blood had no significant changes. Also, a tendency to an increase of bilirubin concentrations in the blood of all experimental animals was also revealed, particularly after an administration of high doses of dimethyl phthalate. Pronounced changes in the weight coefficients of the liver and heart were registered in cases of combined effect.

Significant changes such as granular and fine-dropper fatty dystrophy, foci of discomplexation and necrobiosis of hepatic cells were found in the liver of rats administred with large doses of the two substances. Rabbits had their changes less pronounced and manifested themselves in the form of the organ plethora. Moderate plethora of capillaries of glomeruli and stroma vessels, swelling and granular dystrophy in the epithelium of convoluted tubules could be observed in the kidneys. Dystrophic changes such as lump fragmentation, locallymyolisis were found in the myocardium of rabbits following all series of experiments against the background of diffusion plethora of capillaries. Capillary plethora was registered in all regions of the brain of rats. Individual animals revealed alterations in spermatogenic epithelium followed by the formation of multinuclear gigantic cells and peeling off of the epithelium into the lumens of tubules.

While developing new repellents based on dimethyl phthalate, it is recommended to reduce the quantity of N_1N-diethylamide of phenoxyacetic acid in the composition [37].

Symptoms of total intoxication: a slow increase in the body weight, noticeable leukocytosis of the blood due to increased quantity of segmentonuclear leukocytes developed following a combined effect of toluylpiperidilamide (20%) and dimethyl phthalate (30%) on the skin of rabbits during 50 days (35–36 applications) and following separate applications of these preparations.

Autopsy of the animals slaughtered after the test showed sharp dystrophic changes in the liver (granular and fatty dystrophy), in the kidneys (considerable granular dystrophy in the epithelium of convoluted tubules), in the myocardium (dreary colour of sarcoplasma, locally-lump fragmentation of muscular fascicles).

The enlisted changes appeared to be more pronounced in case of exposure to 100% toluylpiperidilamide. Addition of dimethyl phthalate failed to decrease the toxicity of toluylpiperidilamide, but, on the contrary, even strengthened its toxicity by certain indices [38].

Resorption of diethyl toluamide diluted in dimethyl phthalate was tested on rabbits. The preparation was applied onto the skin at a rate of 7 mg/cm^2. Control animals were applied with pure diethyl toluamide. A much slower transfer of the preparation into the blood from the dimethyl phthalate solution was shown. It is considered reasonable to use lotions containing dimethyl phthalate as a solvent [39].

The toxicity of Benftalat (30% of N- benzoylpiperidine and 70% of dimethyl phthalate), dimethyl phthalate and N-benzylpiperidine were simultaneously tested on white mice. The preparations were intragastrically administered to mice, applied on the skin of rabbits (application

area of 200 cm^2) and of white rats for 26 days at the rate of 1.2 and 0.24 ml/kg.

Following the intragastric administration of the substances the LD_{50} values were equal to 1050 (868÷1270) mg/kg for N-benzoylpiperidine, 4300 (3644÷5074) for dimethyl phthalate, 1850 (1529÷2238) mg/kg for Benftalat. After the skin application LD_{50} accounted for 38 (34.5÷41.42) mg/kg for dimethyl phthalate and 27 (22.28÷31.86) g/kg for Benftalat. The derma-oral coefficient estimated in such test was 9 and 14.6, accordingly. The clinical picture of poisoning following the administration of toxic doses of Benftalat revealed excitation, disorders in movement coordination, occasional clonicotonic spasms, inhibited respiration and death of mice in the course of two days.

Single application of Benftalat on the skin of rabbits did not cause its irritation. Introduction of the preparation into the eyes was followed by lacrimation transforming into hyperemia of the conjuctiva.

Repeated applications of the preparation on the skin of rabbits and rats failed to cause their pronounced response. The animals kept on gaining of the weight throughout the entire experiment. The peripheric blood indices changes within the norm. The quantity of excreted hippuric acid (the Quick-Pyitel test modified by N.G. Stepanova) in tested and control rats appeared to be within the norm. No reduction in the activity of serum cholinesterase was registered. Pathomorphologic investigations failed to reveal deviations from the norm.

The repellent activity of Benftalat against gnats averaged 9 hours 6 minutes ± 30 min. and 8 hours 48 min. ± 32 min., accordingly, in different regions of the USSR (Krasnoyarsk region, Komi ASSR) [25].

The duration of the action repelling gnats, midges and biting midges was found to increase when dimethyl phthalate emulsions (on glycerine and vaseline oil) were coupled with additives of kaolin and fine-powdered chalk [40].

Practical test of complex preparations, containing N,N-diethylamide of phenoxyacetic acid (50%) together with dimethyl phthalate (48%) and enthyl cellulose (2%) such as the Lesnaya preparation or N-benzoylpiperidine (50%), dimethyl phthalate (48%) and ethyl cellulose (2%) as the Zaschita preparation, revealed no intolerance to them. Preparation Zaschita was tested on 1309 persons applied on their face, necks, ears, hands and sometimes on the upper part of the torso. The test resulted in irritation of the skin of the face and mucous layers of the eyes and oral cavity, appearance of erythematous spots and pruritus of the skin. These changes were found in a small number of cases which were associated with the manifestation of individual sensitivity and irritating effect of dimethyl phthalate on mucous membrances.

Trials of the Lesnaya preparation were conducted on 431 persons. No complaints were voiced on the poor health. Visual examination of the tested persons revealed no irritations of the skin. The preparations were applied for 30–45 days. Neither of the preparation appeared to cause the general toxic effect (based on analysis of the peripheric blood and urine).

The repelling duration of dimethyl phthalate was found to be shorter than that of Lesnaya by 1.6 times and that of Zaschita by 1.6 times [41, 42].

Reproduction. The time of spermatozooa mobility was found to remain unchanged after the intragastric administration of dimethyl phthalate to animals on the level of LD_{50} [26].

Application of dimethyl phthalate on the skin of rats in the dose of 10000 mg/kg revealed no changes in the duration of spermatozooa mobility. The quantitative evaluation of the testis morphology showed no verified deviations from the control [30].

The embryotropic effect of dimethyl phthalate was evaluated after an exposure to the skin of rats during the entire pregnancy (19 days) for four hours daily. The preparation was applied in the doses of 10000, 2000 and 200 mg/kg. Rats were examinated and slaughtered to cheek the general toxic and embryotropic effect of the substance on the 20-th day of pregnancy.

No embryotropic effect of dimethyl phthalate (according to the procedure widely accepted in embryology) was revealed as the result of the mentioned experiment.

Alcohol solutions of dimethyl phthalate did not reveal the embryotropic effect either. Analogous negative results were obtained following a second test.

No embryotropic effect of dimethyl phthalate was registered after an intraperitoneal administration of the substance in the doses of 200 and 1000 mg/kg, although pregnant females were noted for having changes in the summation-threshold index.

The posterity (obtained from the tested rats), aged 1, 2 and 3 months, revealed no deviations in their development [30].

Thus, a comparison of the general toxic and embryotropic effects of dimethyl phthalate showed the prevalence of neurogenetic lesions over embryotropic one [30]. There is, however, a report that after a daily applications of dimethyl phthalate on the skin of albino rats in the 1250 mg/kg concentration, conducted from the first to the 19-th day of pregnancy, significant embryotropic effect could be observed together with an increased number of pre- and postimplantation resorption and death of newly-born rats in the postnatal period [15].

There are indications proving disturbances of implantation processes after an intragastric administration of dimethyl phthalate (once or three times) on the 3-rd, 6-th, and 9-th day of pregnancy. Diminished fetus size and weight alongside with other changes were noted herewith [33, 47].

Sensitisation. A moderate sensitizing effect of esters of o-phthalic acid is described both during tests on guinea-pigs and while examining humans [44, 45, 46, 47].

Primary irritation. There are reports concerning the development of a pronounced irritative action of dimethyl phthalate on the mucous layers of the eyes.

Development of conjuctivitis with keratoleukoma could be observed when pure dimethyl phthalate was introduced to the rabbit's eye [13, 15].

In medical practice there are two cases of eye burning with dimethyl phthalate observed. The injured persons complained of colics in the eyes and worsened vision. Eyelids looked very edematic, coupled with blepharospasms, strong photophobia. Edges of the eyeylids appeared to be

hyperemic and transitory folds-anemic. The cornea is dim, locally friable, visual acuity of one victim – 0.02 (the right eye) and 0.01 (the left eye), and 0.7 and 0.8 in another patient. Improvement came on the 4-th day, degeneration of tissues did not occur, hyperemia developed. Keratoleukoma resolved slowly. The visual acuity of the seriously injured person increased to 0.7 and 0.8 and recovered completely in the other [48].

There are reports pointing out to the feeling of the eyes' burning in case different forms of repellent preparations, based on dimethyl phthalate, would get onto the mucous layers of the eye [6, 13, 49, 50, 51, 52].

EFFECTS ON ORGANISMS IN THE ENVIRONMENT

Tests of dimethyl phthalate on rabbits and reindeers revealed the absence of its toxic effect following the skin application of 1–2% emulsion of dimethyl phthalate at a rate of about 200 ml per reindeer [56, 59].

There are reports to the effect that dimethyl- and dibutyl phthalates possess toxic properties for gnats, mosquitoes, louses and other insects including ticks. Ticks were found to develop paralysis followed by death in an hour after they get onto the treated fabric. Clothing, treated with phthalates, remain toxic for ticks for two weeks [55].

A container with a piece of gauze, soaked in dimethyl phthalate, attracted gnats which gathered in its lower section in 20 minutes, but trying to take up they could not reach the upper part. On the second hour their attempts to take up stopped. Gnats, however, did not die even on the 4-th day. Moreover, on the second day of their staying in the vapours of dimethyl phthalate, their behaviour did not differ from that of the control.

After spraying with dimethyl phthalate gnats developed the sticking of wings, extremities and mouth parts. Death arrived only in two days. When the substance was applied only on the back or pads or on the trunk, there appeared flaccidity of the flight, disorders in the coordination of movements. In 3 hours gnats could not repelled, in 4 hours their landing would become flattened, their pads were spread out. The neurotropic effect of the preparation was the strongest after spraying of the trunk, weaker – after spraying the pads negligible – after the back spraying.

Death of females after wetting the trunk arrived in 24–26 hours, pads – in 32–38 hours, the back – in 48–52 hours, i.e. insecticide effect was pronounced weakly.

Vapours of dimethyl phthalate acting via the nerve endings of the sense organs of insects, disorientate the gnat while it approaches the repellent treated man causing irritation. Following a longer effect on the insects, vapours of the substance cause inhibition of the nervous system [60].

In should be noted that the main types of mosquitoes and midges (gnats, midges, biting midges) have different sensitivity to the same repellents – fact that could be proved by the value of the minimum effective dose. The minimum effective dose for midges was proved to be about theer times higher than that for gnats and higher than for mosquitoes by a factor of 10 [12]. Gnats of various species also exhibit

inadequate sensitivity to repellents [65]. It was shown that the effect of dimethyl phthalate vapours is stronger on common malaria mosquito than on Ae eles mosquito. The effect of the preparation on female Ae cinereus is even weeker [60].

While comparing the repellent activity of dimethyl-, diethyl- and dibutyl phthalates in relation to ticks Ixodes persulcatus revealed a more stable repelling (contact) effect in dibutyl phthalate [13].

The acarorepellent effect of dimethyl phthalate towards different stages in the development of Alectorobius tholozanipapilipes tick manifests itself in the doses of 10 and 20 g/m^2 effecting hungry and satisfied larva. Nymphs II, IV and imago (hengry and satisfied) could not be repellent by dimethyl phthalate [64].

SAMPLING / PREPARATION / ANALYSIS

For determination of o-phthalic acid esters a titrometric method, based on saponification of ester by alkali in alcohol medium, has been suggested according to the reaction: [85]

$$RCOOR + KOH - RCOOH + R\,OH$$

Calculation of the phthalate quantity is calculated by the amount of alkali used for saponification, including the formation of methyl alcohol [2].

There are also colorimetric methods of detection, based on obtaining hydroxamic acids to be followed by detection using ferrous chloride [86] and by the reaction with paradimethylaminobenzaldehyde after decomposition of phthalate [87].

These methods are not sensitive enough, non-specific of luminescence analyses [88]. The method is based on a qualitative reaction consisting in decomposition of phthalate with alkali to a salt of phthalic acid, and subsequent obtaining of phthalic anhydride and the latter's fusion with resorcinol.

The formed fluorescein luminesces with yellow-green colour in an alkali medium. This reaction proceeds according to the scheme:

COOR Na OH COONa COOH CO
COOR COONa COOH CO O

Only phthalates produce this reaction.

The minimum amount of the substance detected by the mentioned method is 2 mg in 10 ml. The qualitative determination is possible beginning with 0.005 mg concentration.

When several esters of phthalic acid are present in the air, the most suitable method for their separation and quantitative detection is the chromatographic methods: in a thin layer of sorbent and gas-liquid chromatography.

Esters of phthalic acid from methyl to dodecyl were detected using the gas chromatograph "Shimadzu" with a differential flame-ionizing detector. Consumption of the gas-nitrogen-carrier is 75 ml/min. and 80 ml/min of hydrogen-carrier. The principal chromatographic characte-

ristics of substances under study: the specific and relative retained volumes, dissolution heat, can be calculated.

In the homologic series of complex esters of phthalate acid the logarithm of the specific retained volume value (V_g) is the linear function of the number of carbon atoms (C_x). Having determined the relative retained volume of an unknown plastifier, it is possible to estimate the molecular weight of the unknown complex ester in the above-mentioned conditions using the prior built graph.

Thus esters of dicarbonic acids in all investigated stationary phases are retained practically adequately. The value of dissolution heat is found to have a livear increase with a growth of the molecular weight of symmetric esters of dicarbonic acids. The obtained data make allow to identify complex esters of dicarbonic acids and detect them reliably in case of their migration into the outer medium [89].

A method of thin-layer chromatography is recommended for detection of phthalates. A thin fixed layer of silica gel KSK–3,5 is used with the size of particles 0.01–0.05 mmc when the substances are developed by a solution of recrystallized paradimenthyl aminobenzaldehyde in combination with concentrated sulphuric acid with diethyl ester (1:1). The semiquantitative evaluation is carried out visually by the stain area and the colour intensity, and the quantitative evaluation – by means of a densitometer – in reflected light [90].

A gas-chromatographic method was developed to identify esters of o-phthalic acid by the alcohol radical. During this procedure phthalate is separated, boiled for an hour with two grams of solid KOH and 5 ml of triethylene glycol in a flask with a reverse refrigerator. Insolated alcohols are preserved in an ester layer. Separation and identification of alcohols is conducted on gas chromatograph with katarometer [91].

To detect dimethyl phthalate and its metabolites (monomethyl phthalate and phthalic acid) in biomedia, a procedure of their separate detection in one sample was developed.

Blood samples (not less than 2 ml) were mixed with an equal volume of 3% solution of sodium nitrate, but the organs and tissues were added with 2–3 ml of physiological solution and subjected to homogenization. Then a double volume of extragent (methanole-chloroform 1:2) was added, the sample was divided into two layers – organic solvent and water. The first layer was used for detection of dimethyl phthalate after boiling down, the second for detecting water soluble metabolites of dimethyl phthalate (after acidification by 10% solution of sulphuric acid and extractions by the same solvent).

Detection was conducted by thin-layer chromatography on plates with a fixed layer of silica gel like "Silufol-UF-254". A mixture of chloroform-benzol-ethanole (9:2:1) was used as an eluant. The quantity of detected substances in biomaterial in micrograms per 1 ml or 1 g of substrate was estimated with the help of a calibration curve characterizing the dependency between the stain area on the plate and concentration of the substance by taking the extraction coefficient into account (it ranges from 0.7 to 0.9). Pure dimethylphthalate, phthalic acid and monomethyl phthalate were used as the standard for platting calibration curves. Monomethyl phthalate was synthesized by saponification of dimethyl

phthalate with water-alcohol solution of sulphuric acid, by extraction and its purification with the help of column chromatography on aluminum oxide [16].

TREATMENT OF POISONINGS

Treatment of acute poisonings with dimethyl phthalate should, in the first place, concentrate on the accelerated removal of poison with the urine owing to diuresis increase. In case of acute poisoning it is recommended to make gastric lavage; an aenema (straight after admitting to the clinic), injection of camphor and caffeine, applying of hot water bottle along the entire lenght of the body, giving oxygen [53]. Therapy is conducted with vitamins of B-group, hydrocortisone, aminoacids, glucose with insuline, glucose with strophanthin, adrenaline and physiological solution. Thiopental sodium and aminazine were used to stop spasms and excitation [17]. Ethyl alcohol was administered as an antidote.

Despite the conducted treatment the patients were found to remain in the comatose condition in a number of cases; they would develop symptoms of toxic hepatitis. In connection with that, extracorporeal hemodialysis was carried out by means of instrument AIP–140 with the use of dialyzating solution and with correction of pH of dialyzate. Efficiency of the instrument proved to be 50–250 ml/min. depending on the endurability of the procedure, the duration of which ranged from one to four hours.

Treatment aimed at eliminating sympotoms of toxic hepatitis (glucose, vitamins, hemodes, sirepar, methionine and lipoic acid, antibiotics) was undertaken later on.

Some authors assume that the execution of early hemodialysis, coupled with intensive conservative and antidote therapy, would result in a sufficiently high recovery effect [54].

While conducting the treatment the condition of several patients was found improving progressively. Symptoms of toxic hepatitis, however, remained. Two patients (out of five) developed symptoms of aspiration pneumonia, and one patient developed symptoms of toxic nephritis. The patients were dismissed from the hospital in 2–3 weeks in a satisfactory condition [54].

In case of hard damage of the mucous membranes of the eye, followed by keratoleukoma, the patients' treatment included washing of the eyes with solution of furacin (1:5000), dropping to the eyes of 30% sulfacetamide, solutions with riboflavin, ascorbic acid and glucose, the application of ophthalmic ointment with 10% sulfathiazole. Injections under the eyeball conjuctiva of 0.3 ml of autoblood with 25000 units of penicillin is to be made on the first day of treatment and every other day further on. Drops of 3% dionine were used in the following treatment. This type of treatment results, as a rule, in a complete recovery [48].

RECOMMENDATIONS / LEGAL MECHANISMS

The value of maximum allowable concentration equal to 0.3 mg/m^3 has been adopted as the main hygienic standard of dimethyl phthalate in the air of a working zone [36].

The use of dimethyl phthalate among other repellents is authorized by the USSR Ministry of Public Health [18].

Contraindications to the participation in production where the air is polluted with esters of o-phthalic acid are as follows:

1. Organic diseases of the central nervous system, including epilepsy.
2. Chronic diseases of the peripheric nervous system.
3. Pronounced neuroses.
4. Psychic diseases (even at the remission stage).
5. Pronounced endocrine-vegetative diseases.
6. Clinically pronounced diseases of the liver.
7. Arterial hypertension.
8. Pronounced arterial hypertension.
9. Obliterating endarteritis.
10. Diseases of the blood.
11. Gastric ulcer and duodenal ulcer.

These contraindications should not be considered absolute, i.e. individual approach is required in selecting workers [23].

Regular medical examinations of persons contacting phthalates are carried out by therapists, neuro-pathologists, otorhinolaryngologists and must include a compulsory examination of the state of the nervous system, liver, kidneys, blood [27].

The method of gas-liquid chromatography on the instrument with a flame-ionizing detector is used in the USSR as an analytical method for detection of dimethyl phthalate. Air sampling is conducted with concentrating. The detection limit of the substance is 0.001 mkg in the analyzed volume of a solution; detection error is ±9–13%. The range of measured concentrations is 0.1–15 mg/m^3.

REFERENCES

1. State Standard 8728–77. Plastifiers. Technical Conditions. Moscow, 1978.
2. Lazarev N.V., Levina E.N. Dimethyl Phthalate. In: Harmful Substances in Industry. Vol. II. Organic Substances. Khimiya Publ., Leningrad, 1976, pp. 193–194.
3. Concise Chemical Encyclopaedia. Soviet Encyclopaedia Publ., 1964, vol. 4, pp. 48–50.
4. Concise Chemical Encyclopaedia. Soviet Encyclopaedia Publ., 1964, vol. 3, pp. 811–813.
5. Antonyuk O.K. The Toxicity of Phthalic Acid Esters. In: Hygiene of Utilisation of Polymer Materials and Products Made of Them. Issue No. 1, edited by L.I. Medved. All-Union Research Inst. of Hygiene and Toxicology, Kiev (VNIIGINTOKS), 1969, pp. 302–306.
6. Rachinsky F.Y., Pervomaisky G.S., Chagin K.P. Dimethyl Phthalate as a Repellent against Mosquitoes – Zoologichesky Zhurnal, M., 1951, vol. 30, issue 1, pp. 69–71.
7. Gladkikh S.G. Preparations Repelling Blood-Sucking Insects and Ticks. M., Meditsina Publ., 1964.
8. Aldireva M.V., Gafurov S.A. Labour Hygiene in the Production of Artificial Leather. M., Meditsina Publ., 1980, pp. 71–78.

9. Dremova V.P., Tseitlin V.M., Zhuk E.B., Smirnova S.M. Kinetics of Evaporation of Certain Repellents from Different Types of Fabric. Problems of Disinfection and Sterilization, Collected scientific works. Issue 22, Moscow Research Institute of Vaccines and Serums. M., 1972, pp. 203–208.
10. Tyulenev K.M., Zakharov E.V., Magidson I.A., Altshuler S.V. Means of Combat against Domestic Insects, Repellents, Reticides, Disinfectant Preparations, Surveys. Series: Household Chemical appliances and Problems of their Development. M., 1977, pp. 42–49.
11. Kutsenko A.I., Burinova L.I., Barshtein R.S., Sorokina I.A., Lisenko G.G. Plastifiers. Production of Plastifiers. In: Reference Book on Plastic Materials, Edited by V.M. Kataev, V.A. Popov, B.I. Samsina. M., Khimiya Publ., 1975, vol. 1, pp. 337–342.
12. Tyulenev K.I., Nikitenko T.K., Megidson I.A. Repellents. Protective Means against Flying Insects, Summary Information. Series: Household Chemical appliances and Problems of their Development. M., 1980, pp. 5–27.
13. Potapova A.A., Vladimirova V.V., Sazonova Z.V., Bogdanov V.I. Comparative Tests of Dimethyl Phthalate, Diethyl Phthalate and Dibutyl Phthalate as Repellents. In: Medical Parasitology and Parasitogenic Diseases. M., Meditsina Publ., 1973, No. 6, pp. 692–697.
14. Ivanov V.N., Kosterina E.N., Gaziev G.A., Borisov E.A., Filippova S.A. Mass-Spectrometric and Gas-Chromatographic Analysis of Gas Extractions and Water Extracts from Polyvinyl Chloride Materials. In: Hygiene and Toxicology of High-Molecular Compounds Used for their Synthesis, Abstracts of the VI All–Union Conference, Under general editorship of B.Y. Kalinin, L., 1979, p. 121.
15. Gleiberman S.E., Volkova A.P., Bolandova S.N., Zhukova E.B. Characteristics of the Toxic properties in Dimethyl Phthalate. Problems of Disinfection and Sterilization. Collected scientif. works. Issue 24, M., 1975, pp. 303–307.
16. Gleiberman S.E., Kotova I.A., Nikolayev G.M., Vurchenko V.V. Pharmacokinetics of Dimethyl Phthalate. In: Medical Parasitology and Parasitogenic Diseases. M., 1978, No. 3, pp. 58–63.
17. Pankov A.G., Lyubashova M.N. Acute Poisoning with Dimethyl Phthalate After Swallowing. Collected scien. works, Rostov State Medical Institute. Chair of Judicial Medicine. Rostov-on-Don, 1959, pp. 96–99.
18. Nikitenko T.K., Govorchenko V.I., Koretko T.E., Prokofieva V.G. Investigations of the Biologic Effect of Dimethyl Phthalate. In: Toxicology of New Industrial Chemical Substances, Issue 15. M., 1979, pp. 49–53.
19. Timofievskaya L.A., Aldireva M.V. Experimental and Natural Investigations ot Toxicity of the Series of Phthalate Plastifiers. In: Toxicology and Hygiene of Petro-Chemical Products and Oil-Refining, Second All–Union conference. Yaroslavl, 1972, pp. 206–208.
20. Timofievskaya L.A. Comparative Evaluation of Toxicity of Organo-Phosphorous and Phthalate Plastifiers. In: Problems Labour Hygiene, Occupational Pathology and Toxicology during the Production and Utilization of Organo-Phosphorous Plastifiers. Collected scien. work. Moscow Research Inst. of Hygiene, M., 1973, pp. 83–86.

21. Timofievskaya L.A., Ivanova N.I., Balyinina E.S. Toxicology of Esters of o-Phthalic Acid and their Rating. Gigiena Truda i Professionalniye Zabolevaniya. M., 1980, No 3, p. 25–27.
22. Aldireva M.V., Timofievskaya L.A., Milkov L.E., Kazbekov I.M. Clinical Hygienic and Toxicologic Investigations on the Effect of Plastifiers on the Organism. In: Production and Treatment of Plastic Materials and Synthetic Resins. Collection of Abstracts, 1975, No 3 (115), pp. 63–65.
23. Timofievskaya L.A., Aldireva M.V., Milkov L.E. Toxicology, Labour Hygiene and the Clinical Picture of Poisonings with Plastifiers Used in Production of Polymer Materials. In: Hygienic Significance of Small Intensity Factors in Conditions of Populated Areas and Production. Collected scien. works. Tssue X. M., 1976, pp. 112–117.
24. Timofievskaya L.A., Aldireva M.V., Kazbekov I.M. Experimental Investigations of the Effect of Phthalate Plastifiers on the Organism. Gigiena i Sanitariya, 1974, No 12, pp. 26–28.
25. Potapov A.A., Vladimirova V.V., Kharitonova S.I., Sazonova E.V., Koshkina I.V. Benphthalate as a Reppelent Based on N-benzoylpiperidine for Protection against Mosquitoes. In: Medical Parasitology and Parasitogenic Diseases. M., 1975, No 5, pp. 586–590.
26. Aldireva M.V., Izyumova A.S., Timofievskaya L.A. Problems of Labour Hygiene and Effect of Phthalate Plastifiers on the Organism of Workers Employed in Production of Artificial Leather. In: Labour Hygiene and Condition of Specific Functions in Female Workers Employed in Petro-Chemical and Chemical Industries. Sverdlovsk, 1974, pp. 154–159.
27. Antonyuk O.K. Toxicology of Complex Esters of Phthalic Acid (survey). Gigiena Truda i Professionalniye Zabolevaniya. M., 1975, No. 1, pp. 32–35.
28. Stankevich V.V., Zarembo O.K. Production, Major Properties and Utilization of PVC. In: Current Problems of Hygiene, Utilization of Polyvinyl Chloride (PVC) Materials, M., 1978, pp. 4–22.
29. Komarova E.N., Petrova L.I., Timofievskaya L.A.. Aldireva M.V. Zarembo O.K., Statsek N.K., Kuzmenko N.M. Hygienic Characteristic of Plastifiers as Additives to High-Molecular Compoundd. In: Hygiene and Toxicology of High-Molecular Compounds and Chemical Raw Material Used for their Synthesis, Abstracts ot reports at the Fifth All–Union conference. L., 1975, pp. 114–118.
30. Timofievskaya L.A., Nikitenko T.K., Govorchenko V.I., Strekalova E.E., Klimova T.S., Domshlak M.G., Chirkova E.M. The Ratio between the General and Specific in Biologic Effects of Phthalic Acid Esters. In: Major Problems of Remote After-Effects of Exposure to Occupational Poisons. Collected scient. works. Edited by A.K. Plyasunov and G.A. Pashkova. M., 1976, pp. 40–43.
31. Aldireva M.V., Klimova T.S., Izyumova A.S., Timofievskaya L.A., Influence of Phthalate Plastifiers on the Generative Function. Gigiena Truda i Professionalniye Zabolevaniya, 1975, No 12, pp. 25–29.
32. Timofievskaya L.A., Ivanova N.I. Biologic Action of o-Phthalic Acid Esters (Selectivity of the Effect and Hygienic Rating in Homologic Series). In: All–Union Founding Conference on Toxicology, Abstracts of reports, M., 1980, p. 70.

33. Sheftel V.O. Hygiene and Toxicology of Plastic Materials Used in Water Supply, Kiev, Zdorov'ya Publ., 1981, p. 72.
34. Yurchenko V.V. Cytogenitic Investigation of Mutagenic Properties of Repellents of Dimethyl Phthalate and N,N-diethylamide of Phenoxyacetic Acid. Pharmacologiya i Toxicologiya, M., 1977, No 4, pp.454–456.
35. Yurchenko V.V., Gleiberman S.E. Studies of Remote After-Effects in Using Repellents. Issue III, Investigations of the Mutagenic Properties of Dimethyl Phthalate and N,N-diethylamide of Phenoxyacetic Acid by the Method of Dominant Lethal Mutations. Medical Parasitology and Parasitogenic Diseases. M., 1980, No 1, pp. 58–61.
36. Timofievskaya L.A., Balyinina E.S., Ivanova N.I. The Selective Effect of o-Phthalic Acid Esters. In: Hygiene and Toxicology of High-Molecular Compounds and Chemical Raw Material Used for their Synthesis. Abstracts of the Sixth All–Union conference, Under the general editorship of B.Y. Kalinin. L., 1979, pp. 290–291.
37. Gleiberman S.E., Bolandova S.N., Kemnits O.Y., Merenkova L.N. Toxicology of Repellent N,N-diethylamide of phenoxyacetic Acid (P–203) and its Combinations with Dimethyl Phthalate. Medical Parasitology and Parasitogenic Diseases. M., 1975, No. 6, pp. 693–698.
38. Gleiberman S.E. Toxicological Characteristics of Repellent Toluene-piperidilamide (P–228). Problems of Disinfection and Sterilization. Collected scient. works. Issue 23. M., 1974, pp. 227–231.
39. Gleiberman S.E., Voronkina T.M. Absorption Studies of Repellent Diethyltolyolamide. Medical Parasitology and Parasitogenic Diseases. M., 1972, No 2, pp. 189–197.
40. Shamrai A.F. Results of Utilization of Dimethyl Phthalate for Human Protection in Forest exploitation and Field Works. Problems of Combating against Taiga Mosquitoes and Ticks. Abstracts of reports delivered at Khabarovsk scientific-practical conf. on mosquito abaitment. Khabarovsk, 1956, pp. 28–31.
41. Almasova V.V., Bataev P.S., Stavrovskaya V.I., Aksyenko G.P., Bezzubova V.P., Vorobyeva Z.G., Gladkikh V.F., Zhukova L.I., Zueva N.K., Korogodina Y.V., Klimova L.P., Kryishova A.S., Masiov A.V., Peirs A.E., Sadovskaya G.Y., Speranskaya V.N., Solovei V.Y., Turgins M.E., Shamrai A.F., Shipitsina N.K., Shinkevich M.A. Field Tests of New Repellents. Medical Parasitology and Parasitogenic Diseases. M., 1961, No 4, pp. 457–464.
42. Almazova V.V. Experience of the Wide Application of New Repellents-Repellin-alpha ("Zaschita"–1) and Repellin-betta ("Lesnaya") in 1961. Medical Parasitology and Parasitogenic Diseases, M., 1962, No.5, pp. 587–592.
43. Martson L.V., Sheftel V.S. Investigations of Teratogenic Properties of Polymer Materials and their Components. In: Hygiene and Toxicology of High-Molecular Compounds and Chemical Raw Material Used for their Synthesis. Abstracts of the Sixth All–Union conference, under the general editorship of B.Y. Kalinin. L., 1979, pp. 39–41.
44. Raben A.S., Alekseyeva O.G., Dueva L.A. Experimental Allergic Contact Dermatitis. M., Meditsina Publ., 1970, pp. 152–157.
45. Dueva L.A., Aldireva M.V. Experimental Evaluation of Sensitizing and Skin-Irritation Effect of Phthalate Plastifiers. Giniena Truda

i Professionalniye Zabolevaniya, M., 1969, No 11, pp. 17–19.
46. Kachalai D.P., Baida N.A., Kozintseva P.V., Polyak N.P., Zinchenko D.V., Dyachenko E.I., Orlov N.S., Pakhomov A.A., Gorbachevskaya E.A. The Sensitizing Effect of Dibutyl Phthalate Plastifiers on the Gastro-Intestinal Tract. Vrachebnoye Delo, 1975, No 3, pp. 135–139.
47. Kachalai D.P., Antonyuk O.K., Baida N.A., Dyachenko E.I., Chubarova Z.V., Larionov V.G., Sokolinskaya E.F., Yalkut S.I., Gorbach G.G. Results of the Hygienic, Clinical and Experimental Investigation of Dibutyl Phthalate. In: Hygiene of Utilization of Polymer Materials in Civil Engineering, Kiev, 1973, pp. 129–133.
48. Milrud P.A. Two Cases of Serious Eye Burning with Dimethyl Phthalate, Military-Medical Journal. M., 1962, No. 5, p. 81.
49. Zhukova L.I. Industrial Tests of New Repellents against Mosquito and Ticks Ixodes persulcatus. Medical Parasitology and Parasitogenic Diseases, M., 1964, vol. XXXIII, pp. 537–540.
50. Pavlovsky E.N., Pervomaisky G.S., Chagin K.P. Mosquito (blood-sucking two-winged), its Significance and Measures of its Abaiting, MEDgiz Publ., Leningrad, 1951, pp. 68–73.
51. Lutta L.S. Fight against blood-sucking two-winged Insects in the Conditions of the North, Petrozavodsk, State Publishing House of Karelian ASSR, 1961, pp. 18–23.
52. Vladimirskaya M.I. The Utilization of Dimethyl Phthalate against Blood-Sucking Insects in Taiga in 1951 and 1952, Zoological Zournal. M., 1953, vol. XXXII, issue 6, pp. 1189–1192.
53. Semenov N.N. Rare Case of Poisoning with Dimethyl Phthalate, Rostov State Medical Institute. Collection of scientific works. Rostov-on-Don, 1959, pp. 204–206.
54. Konovalov C.A., Romanov A.N. Initial Hemodialysis in Treatment of Serious Poisoning with Repellents DETA, Benphthalate, Dimethyl Phthalate, "Anesthesiology and Resuscitology. M., M., 1980, No. 2, pp. 54–55.
55. Vashkov V.I. Repelling Properties of Dimethyl Phthalate, Dibutyl Phthalate and Other Compounds in Relation of Gnats, Mosquito and Ticks. Medical Parasitology and Parasitogenic Diseases. M., No. 4, pp. 317–32[illegible]
56. Saveliev D.V., Mezenev N.P. Tests of Repellents and Insecticides for Protection against Midges in Conditions of Far North. Treatment and Prophylactic of Diseases and Fur-Bearing Animals in the Far North, Surveys, vol. XIII, Krasnoyarsk, 1966, pp. 67–79.
57. Cladkikh S.G. Study of Preparations Repelling the Carriers of Transmission of Human Diseases, Medical Parasitology and Parasitogenic Diseases, M., 1953, No. 1, pp. 82–85.
58. Kon V.G., Kachalova E.K. Dimethyl Phthalate as a Chats Repellent. Medical Parasitology and Parasitogenic Diseases. M., 1951, vol. XX, p. 87.
59. Mezenev N.P. The use of Repellents for Protection of Northern Reindeers from Gnats, Conference Reports. Novosibirsk, 1967, pp. 220–224.
60. Kalmikov E.S. Efficiency of Epicutaneous of Dimethyl Phthalate for Individual Protection against Gnats, Midges and Biting Midges. Medical Parasitology and Parasitogenic Diseases, M., 1954, No. 2, pp. 153–158.

61. Gladkikh S.G. Utilization Experience of Substances Repelling Infection Carriers. Military-Medical Journal. 1953, No. 3, pp. 56–59.
62. Smirnov O.V., Suvorov V.S., Bocharov A.P. New Data on the Tests of Certain Repellents of Fleas. Medical Parasitology and Parasitogenic Diseases. M., 1961, vol 30, No. 5, pp. 613–614.
63. Vashkov V.I., Brun M.I., Brikman L.I., Substances Repelling Ticks. Proceedings of Central Scien. Resear. Inst. of Desinfection. Issue 9, M., Medgiz, 1956, pp. 188–193.
64. Smirnova S.N., Dremova V.P. Sensitivity of Different Development Stages of Alectorobius Tholorani Papillipes Ticks to Repellents. Medical Parasitology and Parasitogenic Diseases. M., 1971, No. 1, pp. 45–49.
65. Zhogolev D.T. On Sensitivity to Repellents of Anopheles pulcherrinus theo and Gnats of Other Certain Species. Medical Parasitology and Parasitogenic Diseases. M., 1968, No 4, pp. 493–495.
66. Pervomaisky G.S., Shustrov A.K. Comparative Data on the Repellent Activity of Certain Chemical Preparations. Results of Investigation on the Problem of Midges Abaitment. 1967, pp. 229–231.
67. Monchadsky A.S. Flying Blood-Sucking Two-Winged Insects. Moscow – Leningrad, Publishing House of the USSR Academy of Sciences, 1952, pp. 20–22.
68. Dremova V.P., Markina V.V., Smirnova S.N., Volkova T.V. Efficiency of Repellent Utilization in the Tundra of Krasnoyarsk Region. Medical Parasitology and Parasitogenic Diseases. M., 1973, No. 1, pp. 21–27.
69. Dremova V.P. Effectiveness of Utilization of Certain Repellents for Protection of Oil-Industry Workers from Biting Insects in Tyumen Region. Medical Parasitology and Parasitogenic Diseases. M., 1967, No 1, pp. 60–65.
70. Vashkov V.I., Kerbabayev E.B., Vinogradskaya O.N., Gornostaev G.N., Gudzhabidze G.S., Dremova V.P., Rabinovich M.V., Odinets A.A., Bogdanova R.A., Starikov A.E. Experience in Protection of Oil-industry Workers against Midges in the Taiga of Tyumen Region. Results of Investigation on the Problem, 1967, pp. 240–245.
71. Dremova V.P., Markina V.V., Zvyagintseva T.V. The Procedure of Primary Selection of Repellents in Field Conditions. In: Problems of Disinfection and Sterilization. Collection of Scientific Works. Issue 24, M., 1975, pp. 215–218.
72. Maslov A.V., Shamrai A.F. The Utilization of Repellents for Protection of Workers against Midges. 8-th Conference on Parasitology, Abstracts of Reports. M.–L., Publishing House of the USSR Academy of Sciences, 1955, pp. 96–97.
73. Nizovkin V.K., Pervomaisky G.S., Shustrov A.K. Tests of Repellents in Field Conditions. 9-th conference on the problems of parasitology. Theses of reports. M.–L., Publishing House of the USSR Academy of Sciences. pp. 178–179.
74. Stavrovskaya V.I., Dremova V.P., Kharitonova S.I. Repellent Compositions Designed for the Skin Application, Medical Parasitology and Parasitogenic Diseases. M., 1971, No. 1, pp. 32–36.
75. Potapov A.A. Use of Solid Repellents, Medical Parasitology and Parasitogenic Diseases. M., 1971, No. 1, pp. 32–36.
76. Batayev P.S., Ivanova L.V., Vorobyeva Z.G. New Repellents. Medical

Parasitology and Parasitogenic Diseases. M., 1963, No. 2, pp. 209–216.
77. Rubtsov I.A. Midges in the Europen Part of the USSR and methods of their Abaitment, M.–L., Publishing House of the USSR Academy of Sciences, 1954, pp. 46–51.
78. Safyanov V.M. Test Results on Individual Mosquito-Nets Made of Cloth Impregnated with Repellents in Protection against Attacks of Mosquitoes. Medical Parasitology and Parasitogenic Diseases, M., 1963, vol. XXII, No 5, pp. 549–551.
79. Safyanova V.M., Lu Dgi-en, Jyan Yui-tu. Tests of Certain New Repellents in the Foci of Forest Spring Encephalitis in Kalinin Region. Medical Parasitology and Parasitogenic Diseases, M., Medgiz, 1959, No. 2, pp. 185–188.
80. Gladkikh S.G. Substances Repelling Arthoropoda as the Carriers of Infection Diseases. Journal of Microbiology, Epidemiology and Immunobiology. M., 1953, No. 11, pp. 61–65.
81. Safyanova V.M. Results of Field Tests of Certain Repellents against Mosquitoes (subfamily Phlebotominae). Zoological Juornal. M., 1963, vol. XIII, issue 3, pp. 461–462.
82. Mezenev N.P. Protection of Raindeer Herds from Midges. Veterinariya. M., 1962, No. 9, pp. 67–68.
83. Mezenev N.P. Emulgators for Repellents, Treatment and Preventive Measures against Diseases of Reindeers and Fur-Bearing Animals in the Far North. Scient. Resear. Inst. of Agriculture of the Far North, vol. XIII, Krasnoyarsk, 1966, pp. 81–83.
84. Mezenev N.P. Utilization of Repellents for Protection of Reindeers from Gnats. Chemistry of Agriculture. M., 1966, vol. IV, No. 9, pp. 61–63.
85. Byikhovskaya M.S., Ginsburg S.L., Khalizova O.D. methods of Detecting of Harmful Substances in the Air. M., Meditsina Publ., 1966, pp. 454–455.
86. Kuzmicheva M.N. Detection of Complex Esters (Acetates of Methacrylates) in the Air. Gigiena Truda i Professionalniye Zabolevaniya. M., 1961, No 5, p. 58.
87. Lipina T.G. Colorimetric Detection of Alcohol and Esters. In: New Factors in the Field of Sanitation and Chemical Analysis. M., 1962, pp. 150–157.
88. Vaskevitch D.N. Luminiscence Analysis in Industrial-Sanitation Chemistry. Profizdat Publ., 1956, pp. 71–73.
89. Gortseva L.V. The Chromatographic Behaviour of Esters of Dicarbonic Acids on Various Non-Mobile Phases. In: Utilization Hygiene of Polymer Materials. Abstracts of the Second All–Union conference of sanitation-hygienic control over the utilization of polymer materials in construction, clothing and footwear industries and over the household application of chemicals. Under the general editorship of V.V. Stankevitch. Kiev, 1976, pp. 277–278.
90. Katayeva S.E., Kofanov V.I. Determination of Esters of Dicarbonic Acids in Extracts from Polyvinyl Chloride Films. Gigiena i Sanitariya, 1971, No. 7, pp. 67–69.
91. Kofanov V.I., Gortseva L.V. Gas-Chromagraphic Method of Complex Plastifiers Identification by the Alcohol Radical. Gigiena i Sanitariya. 1974, No. 2, pp. 61–62.

CORRIGENDUM

p. 24, line 32-33, should read

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