Captan: Problems Associated with its Identification in Environmental Materials and Food Products. Potential Solutions.

NATALIYA FEDOROVA, IRINA BEREZNYAK, LYDIA BONDAREVA
Federal Scientific Center of Hygiene named after F.F. Erisman
141014 Moscow
RUSSIA

Abstract: - The study is devoted to identifying the ways in which captan can affect humans, including through the atmosphere and through food. The objects of the research were the following: the active substance (captan), air and a vegetable, namely sweet pepper. The equipment used included a chromato-mass-spectrometer «Agilent 5977A» with a gas chromatograph «Agilent Technologies-7890B», a liquid chromatograph «Agilent 1260» with a diode array detector and a liquid chromato-mass-spectrometer ExionLCAD/Qtrap 6500+. The method of gas-liquid chromatography did not provide reproducible results, due to an unstable connection. Using techniques developed for the identification of captan in air, captan was determined using real samples collected during agricultural work. Captan content was reliably measured using samples taken from the air of the working environment (0,2 – 0,75 $mg \cdot m^{-3}$) and from the skin of operational staff (0,2 – 0,4 mg, using·$wipes^{-1}$). In determining captan content in fruit and vegetable products, new and detailed methodological approaches were developed in order to minimise the matrix effect: a calibration curve was created based on the control matrix sample. The detection limit for captan was established at 0,01 $mg \cdot kg^{-1}$. In the analysis of actual sweet pepper samples, captan content was found to be below the detection limit.

Key-Words: - captan, methodology, chromatography, analytical method, air, food products, real samples
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1 Introduction

Captan is mainly used in agriculture as a contact fungicide. It belongs to the class of phthalimides, e.g. folpet and captafol, that are used for treating domestic trees, grapes, vegetables and decorative plants, as well as for treating packing boxes for food products. It has a protective and remedial effect against a wide range of fungal diseases in fruit, vegetables and decorative plants [1]. Captan is also used in cosmetics (e.g. in antibacterial soap and shampoos) and pharmaceuticals, oil-based dyes, lacquers, wallpaper adhesives, plasticisers, polyethylene, vinyl, stabilisers of natural rubber and textiles [2].

As early as in 1972, German scientists reported captan to have mutagenic effects, i.e. an influence on heredity. The peculiarity of captan, as well as of other pesticides (e.g. DDT), is the ability to accumulate in the fatty tissues of animals and in humans who consume pesticide-containing food (the rule of «biomagnification») [3].

The Environmental Protection Agency (EPA) assigns captan to group B2, "probably carcinogenic to humans" [4]; it can penetrate the human organism as an aerosol upon breathing. In the case of a short-term action, captan has an irritating effect on the skin and eyes [5]. In the case of repeated, or long-term, contact with the skin, captan can cause dermatitis or have a sensibilising effect [6]. During the professional application of chemicals based on captan, for example, in agricultural work, the content of this substance in the air of the working environment can be as high as 0,2 - 0,75 mg/m^3. Eight hours of work, depending on concentration levels, can result in an absorbed inhaled dose of captan reaching 2,4 - 9,0 mg or 0,034 - 0,128 mg/kg depending on body weight [6].

As a rule, the main negative effects of captan occur when the substance enters the body with fruit and vegetables. In some regions of the world, considerable amounts of captan have been revealed in this type of food; for example, the maximum residual amount of captan detected in strawberries sold in the USA was 20 mg/kg [7]. In European Commission (EC) countries, as well as Korea, Australia and China, the maximum residual amount of captan in strawberries has been found to exceed 15 mg/kg [8]. Captan is among a hundred pesticides frequently detected in food. According to the data given in [9], in 2017, about 80 cases of residual amounts of captan were found in food products from EC countries, with its content varying from 0,0064 to 0,855 mg/kg. The content of captan is given as its total content, with its main metabolites being

tetrahydrophthalimide (THPI) and thiazolodine-2-thione-4-carboxylic acid (TTCA) [9].

Because of the current risk of captan entering the body of employees, both during the course of work and with food, the identification of this substance is of great importance for minimising its physical impacts.

Since captan, because of its chemical properties, is rather unstable and tends to decompose, there is the problem of detecting captan in air and food in terms of achieving reproducible results.

Known methods of identifying captan, in a number of vegetable matrices [10-13], are based on using liquid chromatography, (i.e. high-performance liquid chromatography with an ultraviolet detector or mass-spectrometer detector).

Officially accepted methods involve gas-liquid chromatography for detecting captan in apple juice [14], water and soil [15]. Available reliable methods include capillary gas chromatography with electron capture detection (GC-ECD) for the determination of captan in matrices with a high water content, with a limit of quantification (LOQ) of 0,01 $mg \cdot kg^{-1}$, in apples, pears, peaches, nectarines and tomatoes, and electrical conductivity detection (GC-ECD), with LOQ ranging from 0,02 to 0,05 $mg \cdot kg^{-1}$, in apples, tomatoes and fractions of processed tomatoes, where it is possible to apply the multi-residual method QuEChERS, as described in a European standard [16]. The method of capillary gas chromatography with mass spectrometry (GC-MSD) is also used; this method makes it possible to analyse captan residues in matrices with a high-water content, with LOQ being 0,02 $mg \cdot kg^{-1}$ [17]. Almost all the abovementioned methods are known to be complicated by very pronounced matrix effects characterised by a significant increase in the chromatographic signal [18-20].

The conditions of chromatography investigations described in the literature do not allow one to achieve the necessary sensitivity when detecting captan in air that meets the required standards. Moreover, in the process of detecting captan in food, the matrix effect is of great significance, and is not comprehensively studied in the available literature [18-20].

The aim of the study is the development of methodological approaches for detecting residual amounts of captan in the air environment and food products (i.e. some kinds of fruit and vegetables).

2. Materials and methods

2.1 Sample preparation

Captan - 3a,4,7,7a-tetrahydro-2-[(trichloromethyl)thio]-1H-isoindole-1,3(2H)-dione (Fig. 1). CAS 133-06-2; molecular formula: $C_9H_8Cl_3NO_2S$; Formula Weight: 300.6 (Fig. 1).

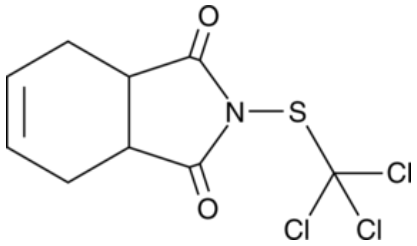

Fig. 1. Structural formula of captan.

In terms of its properties, captan is a colourless powder that has no melting temperature, since it decomposes at 178 °C. Regarding its chemical properties, the most dangerous fact is that, in the process of decomposition, captan releases toxic substances containing sulphur oxide, nitrogen oxides, hydrogen chloride and phosgene [19].

The research materials included atmospheric air and food products, namely sweet pepper.

Air samples were taken according to the requirements of State standards GOST 17.2301-86 [21].

2.1.1 Sub-subsection

2.1.1 Constructing a calibration curve for standard solutions

To construct a calibration curve, use was made of the analytical standard of captan, with the content of the main component being 99,6 %. To prepare the main calibration solution of captan (100 μg/ml), 0,0100 ± 0,0005 g of the active substance was placed into a calibrated flask with a volume of 100 ml. The aliquot was dissolved in 30 ml of acetone, in the case of GLC, or acetonitrile, in the case of HPLC, and made up to volume with acetone or acetonitrile. The storage conditions for the solution were: a freezer, at a temperature not higher than -18 ^{0}C, for no longer than 4 weeks. The working solution of captan for calibration and introduction (10,0 μg/ml) was prepared by diluting the initial calibration solution to a concentration of 100,0 μg/ml; 10,0 ml of the main captan solution was placed into a 100 mL volume calibrated flask. The solution was made up to volume with acetone (for GLC) or acetonitrile (for HPLC) and thoroughly mixed. The storage conditions for the solution were: a fridge, at a temperature of +2 - 6 ^{0}C, for no longer than

1 week. For building the calibration curve, the working solutions of captan were also prepared in 100 ml volume calibrated flasks. For this purpose, 2, 3, 5, 10 and 20 ml of the working solution with a concentration of 10,0 μg/cm^3 were placed into flasks. Depending on the detection method, the solutions were made up to volume either with acetone (GLC) or with the mobile phase (HPLC). The solutions were prepared before each measurement and were not stored.

2.1.2 Sample preparation for the measurements

2.1.2.1 Air samples

Atmospheric air was aspirated, at a volumetric flow rate of 2,0 l/min, through sampling tubes filled with a porous polymer sorbent (XAD-2). To determine the captan at the required level of quantification (0,002 mg/m^3), 50 l of air was sampled. The contents of the exposed sorption tube (sorbent and fibre glass) were placed into a 150 mL volume beaker, filled with 20 ml of acetone and then placed into an ultrasonic bath for 15 minutes. The solvent was removed and the tubes were subsequently treated twice with new portions of 20 ml of acetone and kept in the ultrasonic bath for 10 minutes each. The combined extract was concentrated almost to dryness using a rotation vacuum evaporator at a bath temperature not higher than 40 °C, and the remaining solvent was blown away with a flow of warm air. The residue was dissolved in 0,5 ml of the mobile phase, thoroughly mixed and analysed under conditions set for chromatographic investigation.

2.1.2.2 Samples of vegetables: sweet pepper

The sample of a vegetable, sweet pepper, was first homogenised with a cutter. An aliquot of (10,0 ± 0,1) g was taken from the initial homogenised sample, placed into a 50 ml polypropylene centrifuge test tube, with the addition of 10 ml of acetonitrile saturated with n-hexane, and thoroughly stirred. Then, a mixture of salts for extraction was introduced into the test tube with the mixture containing (4,00 ± 0,01) g of magnesium sulfate, (1,00 ± 0,01) g of sodium chloride, (1,00 ± 0,01) g of tri-sodium citrate and (0,50 ± 0,01) g of di-sodium citrate, 1,5-hydrate and intensively stirred. Subsequently, the mixture was centrifuged for 5 minutes at 5000 rpm at 20 ^{0}C. The supernatant solution obtained was filtered into a vial through a membrane filter (with a pore size of 0,45 μm).

2.2. Methods and conditions of detection

MSD: «Agilent 5977A» equipped with a gas chromatograph «Agilent Technologies-7890B», a capillary column HP-5MSUI 30 m in length and with an inner diameter of 0,25 mm, the sorbent film thickness being 0,25 μm; the volume of the introduced sample was 1 μl.

Liquid chromatograph: «Agilent 1260» («AgilentTechnologies», USA) with an ultraviolet detector (DAD, operating wavelengths of 220, 250 nm), a steel column (250 mm x 4,6 mm), containing ZORBAX Eclipse XDB-C18, 5 μm; acetonitrile – orthophosphoric acid (0,2 %) (60:40 volume). The volume subjected to chromatography was 20 μl.

Liquid chromatography mass-spectrometer: Exion LC AD/Qtrap 6500+ (Malaysia). Ion source: Electrospray (ESI). Electrode voltage: 5500 V. Dryer gas pressure: 60 psi. Dryer gas temperature: 400 ^{0}C. Curtain gas pressure: 25 psi. Operational mode: multiple reaction monitoring (MRM). MRM transitions of captan: 300→264 (for quantitative analysis); 300→265 (confirmation). Column: Synergy Fusion RP 80A, 50 x 2 mm, 4 μm. Eluents: A - 0.1 % formic acid in deionised water, B - Acetonitrile. Elution mode: Gradient. Column temperature: 40 °C. Eluent flow rate: 0.4 ml/min. Volume of the injected sample: 5 μl. Estimated retention time: 3.5 minutes.

3 Results and Discussion

3.1 Methodological approaches to the determination of captan in the air medium

Based on a literature review, the initial option in the development of a method for detecting captan in air was considered to be capillary gas-liquid chromatography with mass-spectrometric detection. Under the given chromatographic conditions, however, it was not possible to obtain the linear dependence of the area of the chromatographic peak on the concentration of the substance in the working solution (Fig. 2). This is probably because captan is an extremely unstable compound and, when heated, it quickly transforms into metabolites.

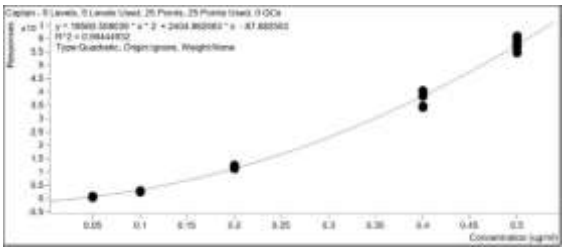

Fig. 2. Dependence of the area of the chromatographic peak on the concentration of captan in the solution. Chromato-mass-spectrometer «Agilent 5977A» with a gas chromatograph «Agilent Technologies-7890B». The *x*-axis shows the concentration of captan, µg/µl. The *y*-axis shows the peak intensity (peak area), mV/s.

As a result, an attempt was made to use high-performance liquid chromatography with a diode array ultraviolet detector, to determine of the concentration of captan in solutions.

Scanning the absorption spectrum of captan in the ultraviolet region (190 - 320 nm) showed the presence of the absorption maximum at 245 nm (Fig. 3). Since the intensity of the maximum was low, it was decided to take a wavelength of 220 nm for further studies, which is acceptable for the detection of the substance, and 250 nm for confirmation.

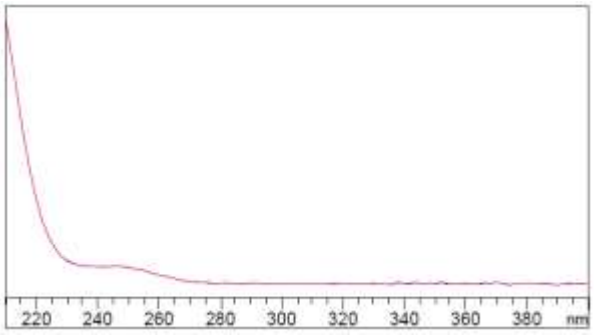

Fig. 3. Absorption spectrum of captan in the ultraviolet region. The *x*-axis shows the wavelength, nm. The *y*-axis shows the optical density, in rel. units.

Simultaneous identification by the presence of peaks in the chromatogram at selected wavelengths made it possible to reliably confirm the presence of captan in the analysed samples. Based on this, a calibration curve was built using two wavelengths (Fig. 4).

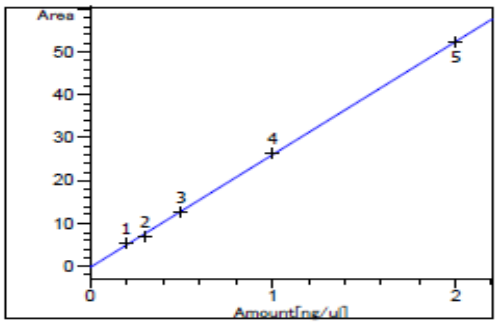

Fig. 4. Dependence of the area of the chromatographic peak on the concentration of captan in the solution. Liquid chromatograph «Agilent 1260» («Agilent Technologies», USA). The *x*-axis shows the concentration of captan, µg/µl. The *y*-axis shows the peak intensity (peak area), mA/s.

For further research in determining the content of captan in the atmosphere, the HPLC method was used. The range of the identified concentration of captan was (0.002 - 1.000) mg/m^3, with SRLI being 0.003 mg/m^3 [22].

Fig. 5 presents a chromatogram of captan isolated in the model experiment for identifying the active substance in air, after its concentration in the sorption tubes XAD-2.

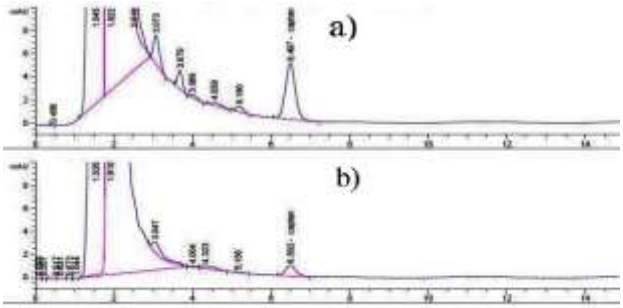

Fig. 5. Chromatogram of captan (1 µg/ml) isolated during the analysis of the model air sample, which corresponded to 1.0 mg/m^3, with 50 ml of air being sampled: a) wavelength - 220 nm, b) wavelength - 250 nm. Liquid chromatograph «Agilent 1260» («Agilent Technologies», USA). The *x*-axis shows time, minutes. The *y*-axis demonstrates the peak intensity (peak area), mA/s.

In this regard, the control was performed in terms of the captan content in the real samples taken in the case of the captan-based agent being used as an active pesticide in agriculture. The application activities included fan spraying of the apple orchard. The results are shown in Table 1.

Table 1. Results of the concentration of captan detection in real air samples and wipes from the skin of agricultural workers.

Sample	Concentration	LOD	State standard
Type of activity – fan spraying			
Atmospheric air, mg/m^3	n.d.*	0.002	0.003 mg/m^3
Air from working area, mg/m^3	0.75-0.15	0.15	0.3 mg/m^3

Washes from skin (μg per wash): Face + neck Breast	0.406 0.347	0.1	-
Type of activity - manual pruning of apple trees			
Atmospheric air, mg/m^3	n.d.*	0.002	0.003 mg/m^3
Air from working area, mg/m^3	n.d.*	0.15	0.3 mg/m^3
Washes from skin (μg per wash): Face + neck Breast	0.244 0.179	0.1	-

* n.d.– the amount of captan was below 0.002 mg/m^3/ 0.15 mg/m^3

3.2 Methodological approaches to the detection of the concentration of captan in fruit and vegetable products - sweet pepper

During the development of the technique for detecting captan in samples of sweet pepper, there arose a problem associated with the matrix effects of the analysed sample. With the calibration graph based on the solutions of the active substance in the organic solvent being used, significantly overestimated results were obtained. In this regard, it was decided to build a calibration curve consistent with the matrix (matrix calibration).

A homogenised mass of sweet pepper was used as a matrix sample for calibration. A number of aliquots were taken from a homogenate sample which did not contain the components under study (hereinafter referred to as a blank sample) and sample preparation was performed according to the procedure described for real samples in the section "Materials and methods - Sample preparation". A blank purified extract was obtained with a total volume of at least 10 ml, to be subsequently used to prepare matrix solutions for calibrating and diluting the samples. Such a sample can be stored in a freezer at a temperature of -18 °C for 3 months.

The matrix sample was placed in a 50 mL volume centrifuge tube and the solution of captan in the organic solvent with a concentration of 10 μg/ml was added in an amount corresponding to the highest calibration level, kept at rest at room temperature for 10 - 30 minutes and then sample preparation was performed according to the procedure described in the section "Materials and methods". The extract with the given concentrations of the substance was obtained in an amount of 3 - 4 ml. Calibration solutions were prepared by serial dilution, using the blank purified extract of sweet pepper as a solvent.

The calibration characteristic, which reflects the dependence of the peak area on captan concentration, was obtained by a calibration method using five calibration solutions (Fig. 6).

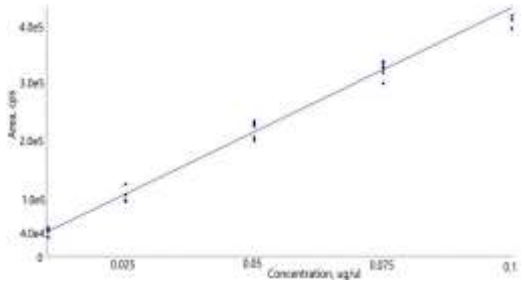

Fig. 6. Dependence of the area of the chromatographic peak on the concentration of captan in the matrix. Liquid chromato-mass-specrometer Exion LC AD/QTrap 6500+. The *x*-axis shows the concentration of captan, ng/mm^3, while the *y*-axis shows the peak intensity (peak area), count/sec.

Fig. 7 presents a chromatogram of captan isolated from a mixture containing eight pesticides

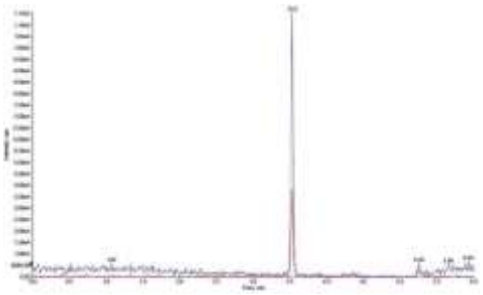

Fig. 7. Chromatogram of captan (0.05 μg/ml) isolated from a mixture of eight pesticides. Liquid chromato-mass-specrometer Exion LC AD/QTrap 6500+. The *x*-axis shows time, minutes. The *y*-axis shows the peak intensity (peak area), count/sec.

The main marker of using captan in agriculture is its detection in air. Specifically, the studies presented in [23] indicate the following. Despite the fact that, in the United States, the application of captan has been declining since 2003, due to its substitution with other chemicals of similar impact, annual recordings of the maximum amount of captan in the air are made in the spring-summer period, which is a period when intense agricultural activity starts. At the same time, one can observe the spread of captan over considerable distances from the location of its application, by atmospheric air flows. It is the aerosols present in the air that play a key role in the

process of atmospheric transport. Captan present in the vapour phase quickly decomposes when exposed to hydroxyl radicals in an air flow. Similar data have been obtained in other countries that have different levels of economic development.

Based on real samples taken in the context of the applied agent containing captan in a concentration of 800 g/kg, the quantity of the substance in the research objects was measured (Table 1). In the air samples, the content of captan was lower than the detection limit for the proposed method. However, the content of captan was reliably found in air samples taken at the working area, as well as in the wipes from the surface of various parts of employees' body. In this case, at least two sources of potential exposure to the skin can be considered: 1) accidental transfer through contaminated gloves; 2) entry of captan in the form of aerosols to open areas of the employees' body, from the air of the working area. The latter mode of captan intake is the most probable, in view of the distribution of the active substance in air.

Different methods were developed for identification of active captan in real samples of sweet pepper, which were received by the Department of Analytical Control Methods from a number of market outlets. In the analysed samples, the presence of captan was not detected, with the content of the substance being lower than 0.01 mg/kg.

In the Russian Federation, there is just one captan-containing (800 g/kg) agent that is officially registered and recommended for application in apple orchards and vineyards [24]. Due to an increase in the volume of imported fruit and vegetable products into Russia, however, there is a threat of captan-containing fruit and vegetables being imported. The studies conducted are extremely relevant in terms of monitoring the content of pesticides in imported products in order to provide the population with safe food (fruit and vegetable) products and, thereby, minimising possible negative risks to public health [25].

Even though the study mentions amounts of captan, along with its main components, THPI and TTCA, its findings are quite important. This is mainly because most products imported worldwide still contain traces of captan. So, having a quick way to detect this substance is crucial to determining whether agricultural and food products are safe for people. It also helps environmental monitoring services respond promptly when they find captan in fish, for example, to reduce its harmful effects.

The standard chromatographic method used in this study provides a fundamental way to analyse substances, but it has some downsides. For instance, predicting how long it takes for substances to appear in the analysis is important, to save time when identifying them, especially when they are not specifically being looked for. In some other research, artificial intelligence models have shown promise and reliability for this kind of analysis. In the current study, however, an insufficient amount of information was collected to enable full use of artificial intelligence.

4 Conclusion

This paper describes a solution to topical problems associated with detection of a pesticide, namely captan, which has extraordinary physical and chemical properties. A technique was developed for the determination of captan levels in atmospheric air, using high-performance liquid chromatography with diode-array ultraviolet detection. The limit of quantification for captan is 0.002 mg/m^3, while the standard value is 0.003 mg/m^3. With the help of the method developed, studies were carried out on real materials; the pesticide featured was being used in actual agricultural situations. It was found that captan is aerosolised and contaminates open skin of employees using the chemical when working in an apple orchard.

Methodological approaches were also developed to prepare for the analysis of sweet pepper samples, by calibrating the dependence of the peak area on substance concentration based on a matrix. These minimised possible errors associated with the effects of colouring and the presence of other impurities and contaminants, including those not declared in fruit and vegetable products. The limit of quantification for captan using the proposed methodological approach was found to be 0.01 g/kg.

The method used offers a universal solution for captan detection, which is suitable for analysing environmental samples and agricultural/food products. It is a powerful tool for ensuring the safety of these items through efficient monitoring by sanitation and environmental control services.

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