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Original scientific paper

Assessing sister chromatid exchanges in human peripheral lymphocytes exposed to tetrachlorvinphos during G_0 phase

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SUMMARY

While pesticides undeniably contribute to enhancing agricultural productivity, the escalating trend in their usage has given rise to a myriad of environmental and public health challenges over time. Tetrachlorvinphos, an organophosphate pesticide deemed potentially carcinogenic by the International Agency for Research on Cancer, is commonly employed to combat flies, mites, and larvae in animals, safeguarding public health in open spaces, and managing pest issues in domestic animals. We aimed to investigate the genotoxic and cytostatic effects of tetrachlorvinphos on human lymphocytes in the G_0 phase of the cell cycle using the sister chromatid exchange (SCE) assay. We found that tetrachlorvinphos increased SCE values at 3 concentrations (5, 25, 50 μM). On the other hand, the increase in SCE values was found to be statistically significant only at the highest concentration (50 μM, $p<0.05$). We also found that the SCE value showed a linear dose-dependent increase ($p=0.005$). We concluded that exposure to tetrachlorvinphos had genotoxic potential on human lymphocytes in the G_0 phase of the cell cycle. Additionally, exposure of cells in the G_0 phase of cell cycle to tetrachlorvinphos was found to have no discernible impact on cell cycle kinetics.

Keywords: pesticides, organophosphates, genotoxic effects, cytostatic effects, sister chromatid exchange assay, G_0 phase

INTRODUCTION

Organophosphates are one of the pesticide groups that are widely used today for many applications, primarily to protect plants and agricultural products against various organisms in order to increase crop yield, and safeguard public and animal health (Jaga & Dharmani, 2003; Stoytcheva, 2011). Although these pesticides play a significant role in increasing agricultural productivity, gradual rise in their usage rate over time has resulted in various environmental and health problems (Ragnarsdottir, 2000). They pose a significant risk of an emergence of long-term effects because organophosphates are absorbed and accumulated in fatty tissues due to their lipophilic nature (Bolognesi, 2003; Katzung et al., 2012; Kwong, 2002). Numerous

studies have consistently indicated an elevated risk of various diseases, such as Parkinson's and cancer, associated with exposure to pesticides such as tetrachlorvinphos (TCVP), while at the molecular level, these substances induce a range of genotoxic effects, including DNA damage and chromosomal abnormalities (Hung et al., 2015; Jamil et al., 2005; Lerro et al., 2015; Li et al., 2015; Narayan et al., 2013; Timoroğlu et al., 2014; Yang et al., 2020). This situation results in general consideration of organophosphates as a threatening factor to human health in the case of chronic exposure through water, air and food contamination. Therefore, determining the potential effects of commonly used chemicals, such as pesticides, on genetic material is of great importance to protect public health and minimize global risks.

TCVP (Figure 1), an organophosphate pesticide classified into Group 2B (possibly carcinogenic) by the International Agency for Research on Cancer (IARC), is generally used for fly, mite, and larva control in animals, protecting public health in open areas, and pest control in domestic animals (Guyton et al., 2015). It is incorporated into powders and flea and tick collars for domestic animals, and is additionally supplemented to feeds for goats, pigs and horses as a larvicide. Occupational exposure to TCVP typically occurs on farmlands during crop application. Additionally, the general population may be exposed to TCVP by various pathways, including contact with domestic pets, ingestion of residues on vegetables and fruits or direct inhalation during routine applications in residential settings (Davis et al., 2008; Cobanoglu & Cayir, 2021). Due to its potential carcinogenicity, the use of TCVP has been prohibited for any purpose in European Union countries. In contrast, its usage is permitted in the United States, but solely for field crops (Guyton et al., 2015; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2017). Although there are some *in vivo* and *in vitro* studies related to TCVP toxicity, data on its toxicity to humans is still limited (Parker, 1985; National Toxicology Program, 1978; Ergun & Cayir, 2021; Cobanoglu & Cayir, 2021).

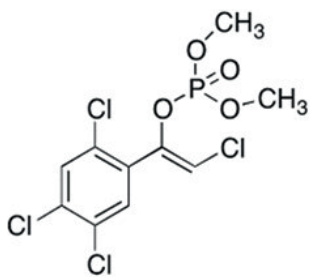

Figure 1. The structure of tetrachlorvinphos

The sister chromatid exchange (SCE) assay is a rapid and sensitive method commonly used in genetic toxicology to assess cytotoxicity and genotoxicity by determining qualitative and quantitative DNA damage. This method allows for a measure of exchange of genetic material between sister chromatids caused by physical, chemical or biological factors. SCE is known as an early indicator of genetic instability (Lialiaris, 2013; Wolff, 1977). That is why the SCE assay has been used in many studies investigating the genotoxic and cytotoxic potentials of various chemicals (Celik et al., 2010; Khabour et al., 2011; National Toxicology Program, 1978). The genotoxic potential of TCVP on circulating human peripheral lymphocytes (HPL) was reported in a previous study (Cobanoglu & Cayir, 2021). On the other hand, no data is available regarding the genotoxic potential of TCVP on human lymphocytes in the G_0 phase of the cell cycle. However, Fenech recommends testing each chemical at different stages of the cell cycle when investigating its genotoxic potential (Fenech, 2000). Therefore, the current study was planned to investigate the genotoxic and cytostatic effects of TCVP on G_0 phase cells using the SCE assay.

MATERIALS AND METHODS

TCVP (99.5 % purity) was obtained from Sigma (USA) and dissolved in dimethylsulfoxide (Merck, Germany, DMSO). Blood samples were taken from 2 voluntary donors (22 and 23 years old) into sterilized heparin tubes. The ethical approval of the study was granted by the Canakkale Onsekiz Mart University Clinical Research Ethics Committee (Decision number: 2021-10).

Controls and concentration ranges

Mitomycin-C (MMC, Sigma, 0.05 μg/ml) was used as a positive control. DMSO was used as a solvent control (<%1, v/v). Kirsch-Volders et al. (2003) suggest that the concentration leading to approximately 50-60% cytotoxicity should be considered as the highest concentration in experimental setups. Therefore, 4 different concentrations (1, 5, 25, 50 μM) were selected as recommended by Kirsch-Volders et al. (2003).

SCE assay

The SCE assay was conducted according to Moorhead's method with minor modifications

(Moorhead et al., 1960). For the preparation of HPL cell cultures, heparinized whole blood should be added to culture medium containing a mitogen, such as phytohemagglutinin (PHA), and incubated at 37 °C for 72 h. SCE formation can be visualized when cells are cultured in the presence of a synthetic nucleoside, an analogue of thymidine, such as 5-bromo-2 deoxyuridine (BrdU), for at least two or more cell cycles. BrdU's incorporation in newly synthesized DNA of replicating cells (S phase) enables visualization and evaluation of SCE. In the present study, each culture was duplicated and was incubated at 37°C for 72 hours. For G_0 exposure, the blood was treated with TCVP (1, 5, 25, 50 μM) for 24 h without phytohaemagglutinin (PHA, Biological Industries, Israel). At the conclusion of the 24-hour period, the cultures were washed three times with medium. Subsequently, the cultures were reestablished using a medium mixture containing PHA. The amounts of 10μg/ml of BrdU (Sigma, USA), and 0.3 μg/ml of colcemid (Biological Industries, Israel) were added to each culture 24 and 70 h after culture initiation, respectively. A KCl amount of 0.075 M was heated at 37°C, and methanol/acetic acid (M/A,3:1) was prepared for harvest (Figure 2). The cells were treated once with KCl and then rinsed 3 times with M/A. Finally, according to Perry and Wolff, the slides were stained with fluorescence plus Giemsa (Perry & Wolff, 1974).

Microscopic evaluation for determining SCE/cell

In the case of each donor and replicate, 25-second metaphases were assessed, with chromosomes stained to distinguish one arm as light and the other arm as dark (Figure 3. b). For each concentration, a total of 100-second metaphases were evaluated (2 donors, 2 replicates) on a light microscope (Olympus, CX31) at 1000 X magnification to determine the mean SCE/cell value.

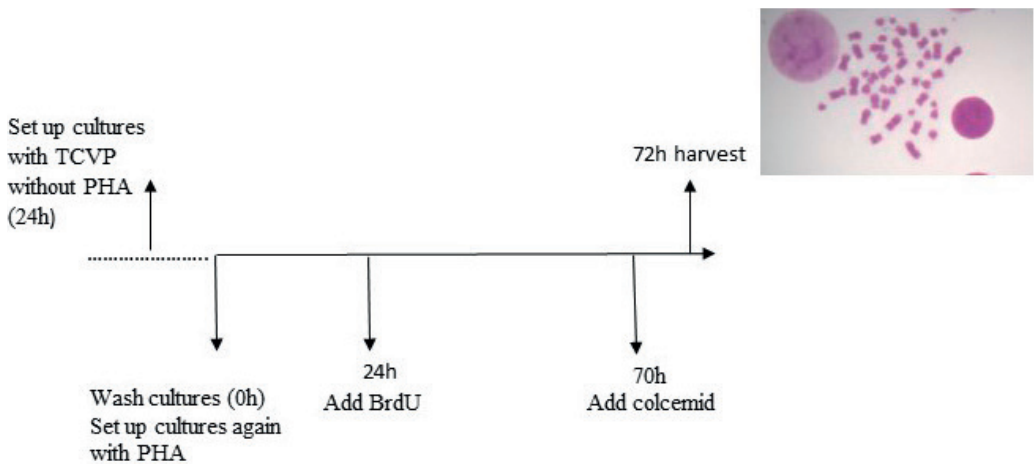

Figure 2. Abstract of experimental design

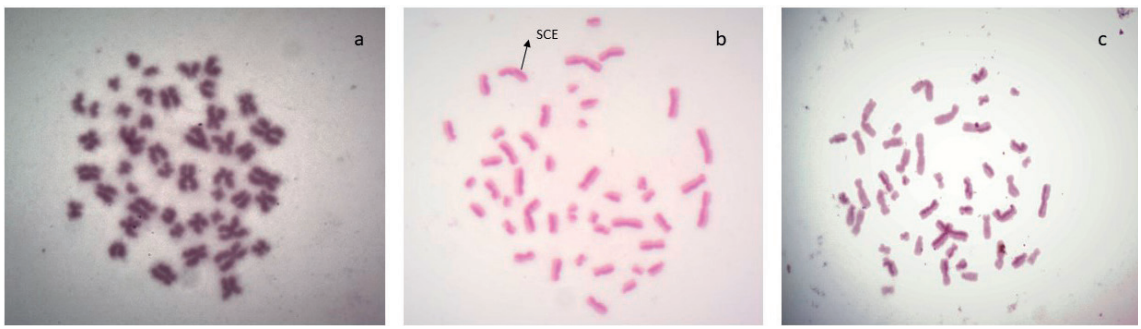

Figure 3. a: first (M1), b: second (M2), c: third (M3) division metaphases

Cytotoxic and cytostatic effects of tetrachlorvinphos

Cytotoxic evaluation for the selected concentrations was performed by mitotic index (MI). While calculating the MI value for each concentration, 1000 cells were scored and the following formula was used:

$$MI = \frac{100 \times \text{cell in metaphase}}{1000}$$

For each concentration, 100 metaphases were evaluated to determine the proliferation index (PI) value representing the cytostatic effect. While calculating the PI values, the following formula was used:

$$PI = \frac{(M1 \times 1) + (M2 \times 2) + (M3 \times 3)}{N}$$

In this formula, M1 (both arms uniformly dark chromosomes), M2 (one arm stained dark, the other arm stained light chromosomes), and M3 (uniformly light and one arm stained dark, the other arm stained light chromosomes) represent the first, second and third division metaphases, respectively (Figure 3).

Statistical analysis

In the study, the statistical analysis of the SCE and PI values was conducted using Kruskal–Wallis and Dunn's multiple comparison tests. A linear regression analysis was performed to show the dose dependence. Data analyses were performed in the Prism software (GraphPad Software Inc) and Excel (Microsoft).

RESULTS

All results are presented as the means (±SE) for two donors and two parallel experiments. Table 1 shows the effect of TCVP on SCE values at four different concentrations. It was found that TCVP increased SCE values at 3 concentrations (5, 25, 50 μM). On the other hand, the increase in SCE value was found to be statistically significant only at the highest concentration (50 μM, $p<0.05$). It was also found that the SCE value showed a linear dose-dependent increase ($p=0.005$, $R2=0.95$). The data obtained for the PI are shown in Table 2. It was determined that TCVP did not change PI values statistically significantly at any tested concentration ($p>0.05$).

Table 1. The effect of tetrachlorinphos on SCE in G_0 lymphocytes

Concentration of tetrachlorvinphos	Metaphase	Mean SCE/cell ± SE
Solvent control	100	4.75 ± 0.14
MMC (0.05 μg/ml)	100	22.50 ± 0.71
1 μM	100	4.75 ± 0.21
5 μM	100	5.03 ± 0.04
25 μM	100	5.27 ± 0.32
50 μM	100	*6.52 ± 0.18

Abbreviations: MMC: mitomycin-C, SCE: sister chromatid exchange, SCE/cell: total number of SCE in a cell, SE: standard error. *$p< 0.05$

Table 2. The effect of tetrachlorvinphos on mitotic index and proliferation index in G_0 lymphocytes

Concentration of tetrachlorvinphos	Cell	Mean MI	Cell	Mean PI
Solvent control	1000	1.67	100	1.69
MMC (0.05 μg/ml)	-	-		-
1 μM	1000	1.68	100	1.70
5 μM	1000	1.62	100	1.69
25 μM	1000	1.61	100	1.65
50 μM	1000	1.60	100	1.65

Abbreviations: MMC: mitomycin-C, PI: proliferation index, MI: mitotic index

DISCUSSION

The current study aimed to investigate whether TCVP has a genotoxic potential in G_0 phase cells. For this purpose, HPLs with more than 95% in the G_0 phase were selected for experiments (Banasik et al., 2005). In the present study, when the SCE values induced by TCVP were compared to the solvent control, it was found that TCVP increased SCE values in a dose-dependent manner. However, a statistically significant increase in the SCE value was observed only at the highest concentration. It was also determined that there was no cytostatic effect of TCVP.

It is well-known that organophosphate pesticides (OPs) can cause DNA damage by interacting with nitrogenous bases or producing reactive oxygen species (Prathiksha et al., 2023). Until now, there have been numerous studies focusing on the genotoxic potential of OP exposure. For example, Garry et al. (1990) demonstrated that malathion induced chromosomal aberration and elevation in SCE on human lymphocytes. In another study, it was revealed that two different OPs, phorate and trichlorfon, caused an increase in SCE and had mutagenic potential on human lymphocytes (Timoroğlu et al., 2014). It was determined that the commercial form of TCVP, named Gardona®, induced a significant increase in chromosome aberrations (Kurinnyĭ & Pilinskaia, 1977). On the other hand, toxicological evaluation of TCVP, a member of OPs, was conducted in only a few human studies (Cobanoglu & Cayir, 2021; Ergun & Cayir, 2021). Ergun & Cayir (2021) investigated whether TCVP caused DNA methylation and cytotoxicity The authors reported that TCVP did not cause DNA methylation but had a cytotoxic effect in A549 lung epithelial cells. Another study reported that TCVP increased micronucleus (MN) frequency on HPL progressing through the cell cycle in all studied concentrations, but that none of these increases were statistically significant (Cobanoglu & Cayir, 2021). In the same study, it was also found that TCVP had no cytostatic effect on HPL progressing through the cell cycle. This finding regarding the cytostatic effect of TCVP is consistent with the findings obtained in the current study. In this context, it may suggest that TCVP does not affect the cell cycle kinetics.

DNA, which is highly sensitive to changes caused by various chemical agents, is the basic unit of heredity. Damaged DNA can play a crucial role in a variety of outcomes, such as genomic instability (Prathiksha et al., 2023). Little is known about the molecular basis of SCE, which represents the exchange of homologous loci during the S phase as a biomarker for genomic instability. It was reported that the target molecules of xenobiotics in the formation of SCE might be the DNA topoisomerase II complex, DNA replication enzymes, and DNA repair enzymes (Wilson & Thompson, 2007; Pommier et al., 1985). A previous study reported that TCVP induced significant changes in SCE values at the three studied concentrations (5, 25, and 50 μg/ml) in cells progressing through the cell cycle (Cobanoglu & Cayir, 2021). On the other hand, in the present study, the SCE value was found to be statistically significant only at the highest concentration. When comparing the results of the two studies, we can speculate two scenarios. Firstly, TCVP might be more genotoxic in HPL cells progressing through the cell cycle than in G_0 phase HPL cells. This possibility would not be surprising because it is expected for cells to be much more sensitive against chemicals when they enter the S, G2, and M phases of the cell cycle (Fenech, 2000). Secondly, for DNA damage to result in SCE, cells must pass through the S phase. Furthermore, the induced lesions can be repaired before the cells enter the S phase (Kopjar & Garaj-Vrhovac, 2000). Therefore, a lesser increase in the frequency of SCE may have been observed in cells damaged in the G_0 phase by TCVP. According to both scenarios, TCVP has genotoxic potential. In addition, we also determined that the SCE value showed a linear dose-dependent increase. The result tells us that longer exposure times to TCVP may be genotoxic in G_0 phase HPLs not only at the 50 μM concentration but also at lower concentrations.

In conclusion, the obtained results showed that exposure to TCVP in the G_0 phase of the cell cycle did not affect cell cycle kinetics. In addition, the results of the current study revealed that TCVP had the potential to induce DNA damage in G_0 lymphocytes, possibly resulting in the formation of SCE. The detection of TCVP's genotoxic potential in the G_0 phase of the cell cycle strengthens the hypothesis presented in a previous study, indicating that TCVP may indeed possess genotoxic properties (Cobanoglu & Cayir, 2021). On the other hand, for a more comprehensive understanding of the molecular mechanisms underlying the potential genotoxic effects of TCVP, future studies could benefit from focusing on specific aspects. First and foremost, exploring whether TCVP triggers oxidative stress, similar to certain other OP pesticides, could

provide valuable insights. Additionally, investigating the capacity of TCVP to bind to DNA warrants attention as it constitutes another pertinent avenue for further exploration.

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Test razmene sestrinskih hromatida u humanim perifernim limfocitima izloženim delovanju tetrahlorvinfosa tokom faze G_0

REZIME

Iako pesticidi nesporno doprinose povećanju poljoprivredne proizvodnje, rastući trend njihovog korišćenja je tokom vremena doveo do pojave raznovrsnih izazova vezanih za životnu sredinu i javno zdravlje. Tetrahlorvinfos, organofosfatni pesticid koji Međunarodna agencija za istraživanje raka smatra potencijalno kancerogenim, koristi se za borbu protiv muva, grinja i životinjskih larvi, u svrhu zaštite javnog zdravlja na otvorenim površinama i suzbijanja štetnih organizama kod domaćih životinja. Cilj istraživanja je bio da se ispita genotoksično i citostatično delovanje tetrahlorvinfosa na humane limfocite u fazi G_0 životnog ciklusa ćelije, koristeći test razmene sestrinskih hromatida (SCE). Našli smo da tri koncentracije tetrahlorvinfosa (5, 25, 50 μM) povećavaju vrednosti SCE. Ipak, to povećanje SCE vrednosti bilo je statistički značajno samo kada je primenjena najviša koncentracija (50 μM, $p<0.05$). Takođe, SCE vrednosti su pokazale linearno povećanje zavisno od doze ($p=0.005$). Zaključili smo da izlaganje humanih limfocita u fazi G_0 životnog ciklusa ćelije delovanju tetrahlorvinfosu ima genotoksičan potencijal. Takođe, izlaganje ćelija u fazi G_0 tetrahlorvinfosu nije imalo primetan uticaj na kinetiku životnog ciklusa ćelije.

Ključne reči: pesticidi, organofosfati, genotoksično delovanje, citostatičko delovanje, test razmene sestrinskih hromatida, faza G_0