Pestic. Phytomed. (Belgrade), 35(3), 2020, 183-191
DOI: https://doi.org/10.2298/PIF2003183C

UDC 632.951:615.9:576.385
Original scientific paper

Assessment of the genotoxic potential of temephos

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Received: 24 September 2020

Accepted: 16 November 2020

SUMMARY

Genotoxic effects of pesticides are of great concern for public health due to the fact that they are widely used for both domestic and industrial purposes. Temephos is a member of organophosphorus pesticides, which is the most widely used group of chemicals against both agricultural and domestic insects. We therefore aimed in the present study to investigate the genotoxic and cytotoxic effects of temephos on human peripheral blood lymphocytes, using the cytokinesis-block micronucleus (CBMN) and sister chromatid exchange assays. The results showed that micronucleus (MN) frequency increased at concentrations of 50 and 75 µg/ml although it was not found statically significant ($p>0.05$). We found that sister chromatid exchange (SCE) values at concentrations of 50 and 75 µg/ml were significantly higher than those obtained for the control ($p<0.01$). We also analyzed associations between temephos exposure and mitotic index (MI), proliferation index (PI), and cell blocked proliferation index (CBPI). There was no significant change in these values at the tested concentrations ($p>0.05$). It can be concluded that temephos was not cytotoxic at concentrations of 25, 50 and 75 µg/ml. However, it may have a genotoxic potential in human peripheral lymphocytes.

Keywords: Pesticide exposure, genetic damage, micronucleus, sister chromatid exchange, cytostatic effect

INTRODUCTION

Pesticides are widely used all over the world as important tools in combating epidemic diseases, increasing crop yield, and protecting forests and plantations. It is estimated that the annual use of pesticides around the world is more than 4 million tons. However, only 1% of the applied pesticides reach target organisms, whereas the rest remains in different parts of the environment. Increasing substantial evidence indicates that many pesticides are potentially dangerous for non-target organisms. The general population can be exposed to pesticides in several ways, including inhalation of contaminated air, dermal administration during medication, or oral intake of contaminated food and water (Bolognesi & Holland, 2016; Grover et al., 2003; Ojha & Gupta, 2015).

Pesticides are the crucial risk factor for non-target organisms such as human beings (Cox & Surgan, 2006; Grover et al., 2003). There are many studies relating to the effects of pesticides on humans, and a great majority of them have focused on the genotoxic effects

of pesticides (Benitez-Trinidad et al., 2015; Cayir et al., 2019; Çayir et al., 2018; Cobanoglu et al., 2019; Grover et al., 2003). This is related to the fact that genetic damage is associated with diseases, including cancer, aging, cardiovascular diseases, and neurodegenerative diseases (Kastan, 2008).

Organophosphorus (OP) insecticides are one of the most widely used groups of chemicals against both agricultural and domestic insects (Rahman et al., 2002). OP pesticides inhibit the hydrolysis of acetylcholine and cause the accumulation of acetylcholine in neuromuscular synapses (Aiub et al., 2002). Temephos is an OP member used as a larvicide to control mosquitoes in ponds and marshes, and swamp midge, black fly and fleas on dogs and cats. Its powder form is used for the control of Pediculus humanus humanus (body lice). It is also used to control mosquitoes in potable water (WHO/HSE/WSH, 2009). Temephos is not approved in EU countries, but it is still in use in most countries around the world (PAN Europe, 2006).

The cytokinesis-block micronucleus assay (CBMN) is one of the standard tests in genetic toxicology which enables measurement of various forms of genetic damage, such as micronucleation (Fenech, 2007). Unrepaired or misrepaired DNA breaks, kinetochore defects, and hypomethylation of centromeric/pericentromeric sequences are known as molecular mechanisms of MN formation (Luzhna et al., 2013). Sister chromatid exchange (SCE) is another cytogenetic marker, and the frequency of SCE increases as a result of exposure to various genotoxic agents. It has been suggested that SCE reflects the repair of DNA damage by homologous recombination (Norppa et al., 2006). Defects in single-strand break repair (SSBR), SSBR-related proteins, and in homologous recombination proteins (HR) are associated with enhanced SCE frequency (Wilson & Thompson, 2007).

Temephos is considered to be harmless for humans (except in contact with skin and ingestion) (WHO/FAO, 2006). So far, several studies have been conducted to assess temephos genotoxicity and cytotoxicity, using different cytogenetic assays. Some of these studies have reported that temephos might be genotoxic (Benitez-Trinidad et al., 2015; Verdin-Betancourt et al., 2019). The novelty of the current study is mainly related to its SCE data. Due to limited and contradictory data, the present study was planned to assess the genotoxic and cytotoxic potential of temephos. Therefore, the present study aimed to investigate the genotoxic, cytostatic, and cytotoxic effects of temephos in human peripheral blood lymphocytes, using the CBMN and SCE assays. For this purpose, micronuclei and SCE frequencies as genetic end-points were measured following the treatment. Besides, we measured the cytokinesis block proliferation index (CBPI) as a cytostatic endpoint. MIs and PIs were calculated to determine cytotoxic effects of temephos.

MATERIALS AND METHODS

Assessment of concentration ranges

Concentrations causing less than 50-60% cytotoxicity were selected as temephos test concentrations in the present study (CAS number: 33833-96-8, Sigma-Aldrich). The cytostatic effect of each concentration was determined by CBPI (Eastmond & Tucker, 1989). The percentage of cytotoxicity were calculated for the concentrations as suggested previously (Lorge et al., 2008).

In vitro CBMN assay

The CBMN assay was carried out as described by Fenech (Fenech, 2007). A culture mixture containing 0.5 ml of whole blood was added to 4 ml of RPMI 1640, 1 ml of fetal calf serum, and 0.2 ml of phytohaemagglutinin (PHA). Two parallel cultures (duplicate cultures) for each donor were set up to represent the selected concentrations of temephos. We added negative and positive controls in each experiment. The cultures were incubated at 37°C for 72 h. Twenty-four hours after culture initiation, the final concentrations of temephos (25, 50, and 75 µg/ml) were added to the culture mixture. A dose of 6 µg/ml of cytochalasin-B was added to each culture 44 h after culture initiation, and the cultures were harvested 72 h after initiation. Microscopic evaluation of the slides was conducted at 1000 x magnification according to Fenech's criteria (Fenech, 2000). For each donor and concentration, 1000 binucleated cells were evaluated to determine MN frequency (Figure 1).

In vitro SCE *assay*

The lymphocyte cultures were set up according to Moorhead's method with minor modifications (Moorhead et al., 1960). The whole blood cell culture mixture was set up with 4 ml RPMI 1640, 1 ml of fetal calf serum, 0.2 ml of phytohemagglutinin (PHA), and 0.5 ml of the blood sample. The cultures were incubated

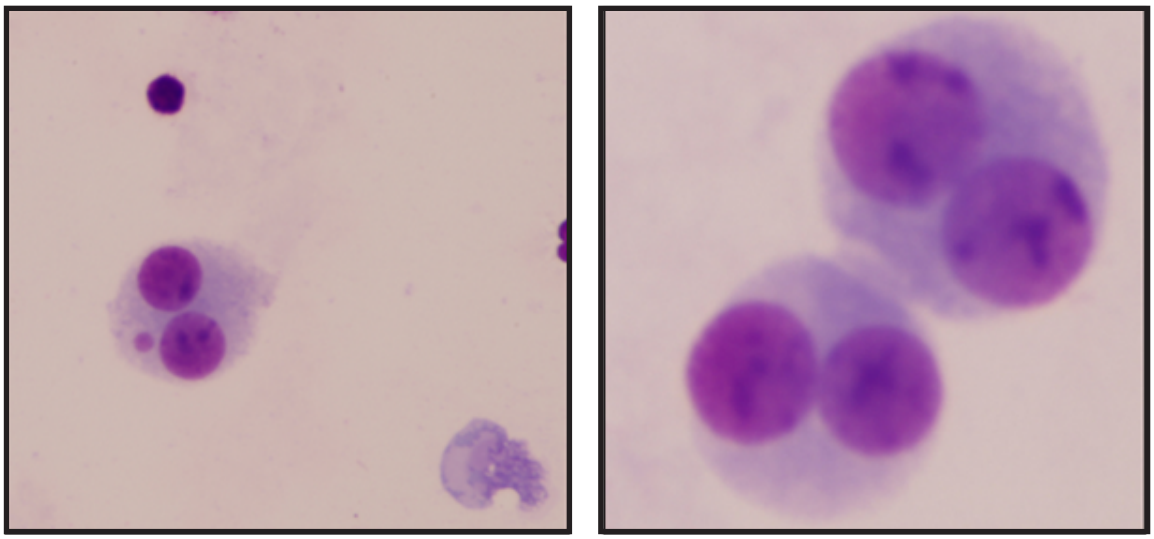

Figure 1. Binucleated lymphocytes with and without micronucleus

in the dark at 37 °C for 72 h. Temephos (25, 50, and 75 μg/ml as final concentrations) and 5-Bromo-2-deoxyuridine (10 μg/ml) were added to each culture 24 h after culture initiation. Two hours before harvesting the culture (at hour 70), 0.1 μg/ml of colcemid was added to each culture. The slides were stained with fluorescence plus Giemsa (FPG) (Perry & Wolff, 1974). Microscopic examination was carried out at 1000 × magnification.

Cytostatic and cytotoxic effects of temephos

The cytotoxicity of temephos was determined by MI and PI, and its cytostatic effect by CBPI. MI values were calculated by counting a total of 1000 cells for each concentration using the following formula:

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

PI values were calculated by examining 100 metaphases for each concentration, using the formula below. In that formula, M1 represents the number of uniformly dark stained chromosomes (Figure 2); M2 represents the number of differentially stained chromosomes (Figure 2); M3 represents the number of uniformly light and differentially stained chromosomes.

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

In total, 500 cells per each concentration were examined to calculate CBPI. For the calculation of CBPI, the following formula was used:

$$CBPI = \frac{(M1 \times 1) + (M2 \times 2) + (M3 \times 3) + (M4 \times 4)}{N}$$

In this formula, M1, M2, M3, and M4 represent the number of the cells with 1, 2, 3, and 4 nuclei, respectively, whereas N is the total number of cells scored. Cytotoxicity percentage was calculated for each concentration as follows: % cytotoxicity = 100-100 [(CBPIT-1) / (CBPIC-1)]. In this formula, CBPIC and CBPIT represent the control and treated cultures, respectively (Lorge et al., 2008).

Statistical analysis

The results are presented as means (±SD) of the two parallel experiments. The obtained results for MN, SCE, MI, PI, and CBPI per concentration of temephos were compared with the negative control using one-way analysis of variance (ANOVA) with Dunnett's multiple-comparison tests. Data analyses were performed in the Prism software (GraphPad Software Inc) and Excel (Microsoft).

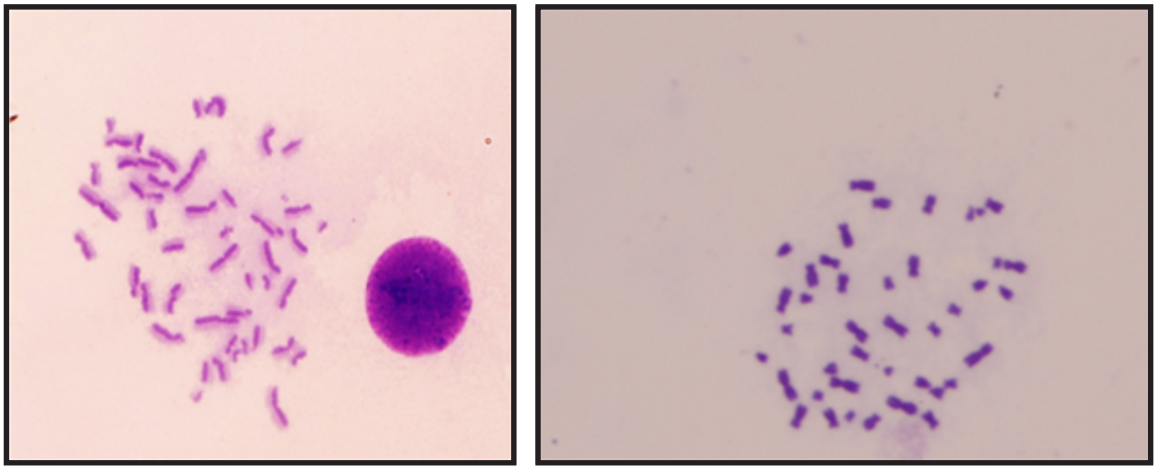

Figure 2. First and second division metaphases

RESULTS

Table 1 shows the effects of temephos on MN frequencies. The results showed that MN frequency increased at 50 and 75 μg/ml of temephos. However, a statistically significant level was not found ($p>0.05$). The SCE frequencies following treatments are presented in Table 2. It shows that temephos caused an increase in SCE frequency at all concentrations. Furthermore, SCE frequencies at 50 and 75 μg/ml of temephos were found to be statistically significant, compared to the negative control ($p<0.01$). We present the effects of temephos on MI, PI, and CBPI values (Tables 2, 3 and 4, respectively). It was observed that temephos did not significantly alter these values at any concentration (25, 50, and 75 μg/ml) ($p>0.05$).

Table 1. Effects of temephos on MN in peripheral lymphocytes

Temephos (μg/ml)	BN cell	Donor A ‰ MNL	Donor B ‰ MNL	Mean ± SD MNL
NC	4000	34.5 ± 0.70	23.0 ± 2.83	28.8 ± 6.85
25	4000	33.5 ± 0.70	23.5 ± 2.12	28.5 ± 5.92
50	4000	36.0 ± 0.00	24.5 ± 0.71	30.3 ± 6.65
75	4000	35.0 ± 1.40	24.0 ± 1.41	29.5 ± 6.45
MMC	4000	156 ± 5.70	119 ± 12.7	137 ± 22.8

BN: bi-nucleated, SD: standard deviation, NC: negative control, MMC: mitomycin C, MNL: total number of micronuclei in lymphocytes

Table 2. Effects of temephos on SCE and PI in peripheral lymphocytes

Temephos (µg/ml)	Donor A SCE/M	Donor B SCE/M	Donor A PI	Donor B PI	Mean±SD SCE/M	Mean±SD PI
NC	5	4.3	1.7	1.6	4.7 ± 0.27	1.7 ± 0.1
25	5.3	4.7	1.9	1.6	5.0 ± 0.54	1.8 ± 0.2
50	7	6.1	1.9	1.8	6.6 ± 0.04*	1.9 ± 0.1
75	7	6.2	1.8	1.8	6.6 ± 0.37*	1.8 ± 0.0
MMC	29	25	-	-	27 ± 1.41	-

SCE: sister chromatid exchange, NC: negative control, MMC: mitomycin C, SD: standard deviation, PI: proliferation index* p<0.01

Table 3. Effects of temephos on MI in peripheral lymphocytes

Temephos (µg/ml)	Donor A ‰ MI	Donor B ‰ MI	Mean ± SD ‰ MI
NC	6.6	6.2	6.4 ± 0.3
25	6.8	6	6.4 ± 0,6
50	8.6	5.7	7.2 ± 2.1
75	6.2	5.8	6.0 ± 0.3
MMC	-	-	-

MI: mitotic index, SD: standard deviation, NC: negative control, MMC: mitomycin C

Table 4. Effects of temephos on CBPI in peripheral lymphocytes

Temephos (µg/ml)	Counted cell number	Donor A CBPI	Donor B CBPI	Mean ± SD CBPI
NC	2000	1.42 ± 0.10	1.49 ± 0.01	1.45 ± 0.07
25	2000	1.49 ± 0.13	1.45 ± 0.01	1.47 ± 0.08
50	2000	1.46 ± 0.03	1.52 ± 0.04	1.49 ± 0.05
75	2000	1.41 ± 0.01	1.39 ± 0.01	1.40 ± 0.01
MMC	2000	-	-	-

CBPI: Cytokinesis Block Proliferation Index, SD: standard deviation, MMC: mitomycin C

DISCUSSION

In the present study, the genotoxic and cytotoxic potential of temephos in cultured human peripheral lymphocytes was investigated. The results showed that temephos caused a statistically significant increase in SCE frequency (at concentrations of 55 and 75 μg/ml). However, it did not significantly increase MN formation. Temephos did not cause a statistically significant decrease in MI, PI, and CBPI values at the tested concentrations. There are several studies that evaluated the genotoxic potential of other OP pesticides. Shadnia et al. (2005) investigated the genotoxicity and oxidative stress caused by commercial formulations of OP insecticides. The authors reported that chronic exposure to OP insecticides induced DNA damage and resulted in a significant increase in oxygen-free radical scavenging enzymes. Similarly, it has been reported that chronic or subchronic exposure to OP insecticides induced oxidative stress (Akbel et al., 2018; Akhgari et al., 2003; Possamai et al., 2007; Ranjbar et al., 2002, 2005).

The addition of temephos to drinking water has been reported to increase the risk of acetylcholinesterase inhibition in human red blood cells. High toxic potential of temephos was also reported (Verdin-Betancourt et al., 2019). The genotoxic and cytotoxic potential of temephos in human peripheral lymphocyte and hepatoma cells (HepG2) were evaluated using the CBMN and comet assays (Benitez-Trinidad et al., 2015). The authors reported that temephos did not show cytotoxic effects in human lymphocyte (0.5, 1, 5, and 10μM) or in HepG2 (0.5, 1, 2, 5, and 10μM) cells. They also indicated that temephos did not significantly increase MN frequencies in human lymphocytes. In our study, temephos was not found to induce any cytotoxic effect or MN formation at a significant level in human peripheral lymphocytes at the concentrations of 25, 50, and 75 μg/ml. Our results are consistent with findings published by Benitez-Trinidad et al. (2015). On the other hand, the authors also reported that temephos increased MN frequency to a significant level in HepG2 cells. It was suggested that the metabolites of temephos might be more genotoxic (Benitez-Trinidad et al., 2015).

To the best of our knowledge, there has been no published data related to SCE formation induced by temephos in human peripheral lymphocytes. As a result of our study, SCE frequency at the concentrations of 50 and 75 μg/ml were found to be statistically significant. SCE occurs during DNA replication as a result of a fracture in sister chromatids and recombination of the fractured region (Wilson & Thompson, 2007). Pommier et al. (1985) reported that DNA intercalators targeted DNA topoisomerases II enzymes. They also indicated that SCE was related to DNA topoisomerases II-induced DNA cleavage. According to the hypothesis, temephos might be considered to be a DNA intercalator targeting topoisomerases II enzymes because of significantly increasing SCE frequency.

Benitez-Trinidad et al. (2015) reported that temephos increased DNA damage derived from single and double-strand breaks. Similarly, it was reported that temephos produced dose-dependent DNA damage measured by the comet assay in blood cells of Wistar rats. These findings and the results of the present study suggest that temephos might have clastogenic effects (Aiub et al., 2002).

In conclusion, the results obtained from the present study showed that temephos might be genotoxic considering SCE formation. Temephos did not induce MN formation. Similarly, temephos did not alter cytotoxicity measured by MI, PI, and CBPI. Due to the molecular mechanisms of SCE, the significant increase in SCE frequency suggests that temephos might have clastogenic effects. In order to clarify this issue, future studies should be designed by FISH staining in MN and/or COMET techniques. Exposure to some chemicals leads to DNA damage directly and/or to other mechanisms, such as oxidative stress (Lebailly et al., 1998). It had been demonstrated in previous studies that OP insecticides induced oxidative stress. We suggest that oxidative stress might be a factor for the genotoxic potential of temephos. In future studies, the genotoxicity of temephos should be investigated by other techniques, such as comet assay with enzyme treatment, which enables measurements of oxidative stress. Furthermore, epigenetic mechanisms, telomere length, etc., could be investigated in future studies.

ACKNOWLEDGEMENT

This work was supported by the Scientific Research Coordination Unit of the Çanakkale Onsekiz Mart University (Project number: FBA-2018-1387).

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Ocena genotoksičnog potencijala temefosa

REZIME

Genotoksično delovanje pesticida na javno zdravlje je od velikog značaja zbog široke upotrebe takvih hemikalija u domaćinstvu i industriji. Temefos pripada organofosfornim pesticidima, koji čine najzastupljeniju grupu hemijskih sredstava koja se koriste za suzbijanje insekata u poljoprivredi i domaćinstvima. Otuda je cilj ovog istraživanja bio da se ispita genotiksični i citotoksični uticaj temefosa na kulturu humanih limfocita periferne krvi, koristeći mikronukleus test sa blokiranom citokinezom (CBMN) i test razmene sestrinskih hromatida (SCE). Rezultati su pokazali da se brojnost mikronukleusa (MN) povećava na koncentracijama od 50 i 75 µg/ml, mada nije ustanovljena statistički značajna razlika ($p>0.05$). Vrednosti SCE na koncentracijama od 50 i 75 µg/ml bile su značajno više u odnosu na kontrolu ($p<0.01$). Takođe smo analizirali i odnose između tretmana temefosom i indeksa mitoze (MI), indeksa proliferacije (PI) i indeksa proliferacije pri blokiranoj citokinezi (CBPI). Nije uočena značajna razlika u ovim vrednostima na testiranim koncentracijama ($p>0.05$). Može se zaključiti da temefos nije bio citotoksičan na koncentracijama od 25, 50 i 75 µg/ml. Ipak, genotoksični potencijal u humanim limfocitima periferne krvi se ne može isključiti.

Ključne reči: izlaganje pesticidima, genetska oštećenja, mikronukleus, razmena sestrinskih hromatida, citostatičko delovanje