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REVIEW ARTICLE

Dimethoate induces genotoxicity as a result of oxidative stress: in vivo and in vitro studies

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Abstract

Dimethoate ([*O*,*O*-dimethyl *S*-(*N*-methylcarbamoylmethyl) phosphorodithioate]) is an organophosphate insecticide and acaricide widely used for agricultural purposes. Genotoxicity refers to the ability of a chemical agent interact directly to DNA or act indirectly leading to DNA damage by affecting spindle apparatus or enzymes involved in DNA replication, thereby causing mutations. Taking into consideration the importance of genotoxicity induced by dimethoate, the purpose of this manuscript was to provide a mini review regarding genotoxicity induced by dimethoate as a result of oxidative stress. The present study was conducted on studies available in MEDLINE, PUBMED, EMBASE, and Google scholar for all kind of articles (all publications published until May, 2020) using the following key words: dimethoate, omethoate, DNA damage, genetic damage, oxidative stress, genotoxicity, mutation, and mutagenicity. The results showed that many studies were published in the scientific literature; the approach was clearly demonstrated in multiple tissues and organs, but few papers were designed in humans. In summary, new studies within the field are important for better understanding the pathobiological events of genotoxicity on human cells, particularly to explain what cells and/or tissues are more sensitive to genotoxic insult induced by dimethoate.

Keywords Dimethoate · Genotoxicity · Mutagenicity · Genetic damage · Omethoate · DNA damage · Responsible Editor: Mohamed M. Abdel-Daim

Introduction

Dimethoate ([*O*,*O*-dimethyl *S*-(*N*-methylcarbamoylmethyl) phosphorodithioate]) is an organophosphorous compound widely employed in agriculture as insecticide (Van Scoy et al. 2016). It was registered in 1962 for use being destined to control a wide range of insects, as for example plant hoppers, mites, flies, and aphids (Dissanayake et al. 2021). To date, dimethoate has been applied to crops such as, grain, fruit, and vegetables (Badry et al. 2021; Van Scoy et al. 2016). Furthermore, the insecticide has been used for non-agricultural purposes, as for example landscape maintenance and pest control (Van Scoy et al. 2016).

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Genotoxicity is the pathobiological phenomenon characterized by genetic damage (Ribeiro et al. 2017). This means that harmful agent is classified as genotoxic if it is able to injury the genetic material. To date, several compounds either from endogenous or exogenous sources are identified as genotoxic in the scientific literature (Ribeiro et al. 2017). For this reason, it is assumed that different agents present in the environment continuously damage DNA molecule either to humans or to other species. Herein, it is very important to investigate what agents are able to induce genetic damage under different end-points and paradigms, especially those in close contact with humans and other species for long time. This scientific knowledge is very important since it protects living organisms against potential harm.

It is well discussed in literature that oxidative stress can activate a variety of pathways that leads to an oxidative imbalance damaging mammalian cells and, after extended periods, promote carcinogenesis (Quezada-Maldonado 2021; Reuter et al. 2010). The increase of ROS may be due to endogenous oxidative stress, from hepatic metabolism and the action of the enzyme P450, mitochondria activities or from NADPH enzymes, or from exogenous origin, such as those

generated by chemical substances (Klaunig 2018). ROS molecules are involved in genotoxicity as a result of gene mutations on injured cell or by its interference in transduction and/or transcription factors (Klaunig 2018).

It is well known that dimethoate is very soluble in water and, therefore, it possesses soil persistence as a result of good properties closely related to good efficacy and fast degradation (Lima do Rego et al. 2021; NPIC 2019). In this context, the environmental consequences of dimethoate are of great concern.

To the best of our knowledge, few review articles regarding dimethoate toxicity are being published with certain regularity. Even so, these papers do not discuss genotoxicity as a result of oxidative stress (Reuber 1984; Van Coy et al. 2016; EFSA 2018). Particularly, little information has been available on the impact of dimethoate as well as its relevant metabolites focusing the side effects on human health. For this reason, further understanding on the impact to the human health for mitigating the noxious activities induced by dimethoate is important to protect humans and other species against potential harm. Herein, a search of the scientific peer-reviewed literature on dimethoate toxicity will provide new insights into the pathobiological mechanisms induced by the insecticide in mammalian cells. These data are relevant not only for the regulators, but also the policy makers.

Taking into consideration the genotoxicity as a result of oxidative stress may be induced by dimethoate, the aim of this study was to provide a mini review taking into account four aspects: (i) the publications over the years, (ii) the test-system used, (iii) the main findings published, and (iv) the identification of gaps within the field, in order to purpose future perspectives, whose goal is to protect humans against potential harm.

Material and methods

The search of the scientific literature was conducted to MEDLINE, PUBMED, EMBASE, and Google scholar for all kind of articles (all publications to May, 2020) using the following key words: dimethoate, omethoate, DNA damage, mutagenicity, mutation, genetic damage, oxidative stress, and genotoxicity. No time limit was imposed to the search, whose goal was to identify the maximum number of papers published within the field. Case reports, papers not written in English language, and reviews were not included to the study.

Results

Genotoxicity

A total of 79 papers were achieved between 1983 and 2020, but only 55 fulfilled the requirements adopted in this setting (Fig. 1). In 1983, a total of three papers were published within the field. Among them, Woodruff et al. (1983) did not detect the presence of chromosome loss in *Drosophila melanogaster*. The insecticide did not induce a significant amount of ring chromosome loss. In the same year, Nehez et al. (1983) evidenced the presence of micronucleated cells in bone marrow cells from mice exposed to dimethoate. However, this finding was not confirmed by Degraeve and Moutschen (1983), since negative results were found in rat by means of dominant lethal assay. All published articles rescued in the scientific searching are shown in Table 1.

Taking into account the papers published using mammalian eukaryotic cells, the majority of studies were performed using experimental test system, in particular rodents (rat and mouse). It is important to highlight that only 7 papers were published in humans, whereas 18 papers were published to animal experimental models. Among them, human lymphocytes are the preferred cells to evaluate the genotoxicity induced by dimethoate. For example, an earlier study conducted by Kizilet et al. (2019) has detected an increase of micronucleated cells in human lymphocytes continuously exposed to dimethoate. These findings were confirmed by others (Kizilet et al. 2019; Undeger and Basaran 2005; Jamil et al. 2004).

On the other hand, it has revealed that dimethoate is able to increase telomere length (Wang et al. 2019; Duan et al. 2017) as well as to induce abnormal expression of some cell regulatory proteins, such as p53 and 21 (Duan et al. 2017). Using single cell gel comet assay as a very sensitive assay for detecting DNA strand breaks. Samarawickrema et al. (2008) showed that dimethoate induces genetic damage in cord blood cells (Samarawickrema et al. 2008). Conversely, a weak genotoxicity has been verified by Bianchi-Santamaria et al. (1997) in human lymphocytes. Taken as a whole, it seems that dimethoate is able to induce genetic injury in humans, as a result of DNA strand breaks.

When performing the use of experimental models in rodents for evaluating the genotoxic potential of the insecticide, several studies have been detected so far. Some studies have demonstrated that dimethoate is able to induce genetic damage being closely associated with oxidative stress in liver and brain cells of rats (Yahia and Ali 2018; Li et al. 2016; Astiz et al. 2009a,b). Other authors have also detected the presence of genetic damage in rat peripheral lymphocytes as well (Qi et al. 2017). In mice exposed to several doses of dimethoate, an increased number of micronucleated cells was noticed (Undeger et al. 2000; Nehez and Desi 1996; Geetanjali et al. 1993). Moreover, lipid peroxidation and subsequent DNA injury in liver and kidney cells were found in mice exposed to dimethoate (Ayed-Boussema et al. 2012b). Such findings are in agreement with others (Dedek et al. 1984).

When *Oncorphydus muykiss* were investigated, genotoxicity and lipid peroxidation were also detected in liver

Table 1 Publications regarding genotoxicity induced by dimethoate in alphabetical order

Author(s)	Year of publication	Country	Experimental test system	Dose	Main findings	Journal ranking (Scimago Quartile)
Ahmad et al.	2014	India	Allium sativum	100 and 200 μg/mL	↑chromosomal aberration in plant cells	-
Aleem and Malik	2005	India	E Coli	1.9–14 ng/L	↑ mutations and interference with DNA repair system	Q1
Anjum and Malik	2013	India	E. coli	2.92 ng/L	↑ mutations	Q1
Ansari and Malik	2009a	India	E. Coli	0.57 ng/kg	↑ mutations and interference with DNA repair system	Q1
Ansari and Malik	2009b	India	E. Coli	0.78–0.99 ng/L	↑ mutations	Q2
Astiz et al.	2009b	Argentina	Rat	15 mg/kg	↑ lipid peroxidation, apoptosis and DNA damage in liver and brain	Q1
Ayed-Boussema et al.	2012a	Tunisia	Mice	1–30 mg/kg	↑ micronucleated cells and chromosomal aberration and DNA damage in boné marrow	Q3
Ben Amara et al.	2013	Tunisia	Rat	0.2 g/L	↑ DNA damage in kidney cells	Q2
Benting and Nauen	2004	Germany	Myzus persicae Sulzer and Aphis gossypii Glover	2.5 μL/cm	↑ mutations in the Acht gene	Q1
Bianchi et al.	1994	Italy	Saccharomyces cerevisiae	50–-10,000 μg/mL	I↑ DNA damage in bacteria	Q1
Bianchi-Santamaria et al.	1997	Italy	Human	0.1 μg/ml;	Weak genotoxicity in lymphocytes	Q1
Cardoso et al.	2017	Portugal	Folsomia candida in soil	0.4–1.6 mg/kg	↑ DNA damage in hemolymph	Q1
Carletto et al.	2010	France	Aphis gossypii Glover	6.4–90 μg/mL	No changes in the Acht gene	Q1
Cunminghan et al.	1994	USA	Rat	250–500 ppm	No proliferative changes in liver and kidney	-
Dedek et al.	1984	Germany	Mice	0.06–0.55 mmol/kg	↑ DNA damage and methylation in liver na kidney	-
Degraeve and Moutschen	1983	Belgium	Rat dominant lethal	10 mg/kg 0.6 ppm	Negative results in germinative cells	Q1
Deshpande et al.	2001	India	Pseudomonas aeroginosa	0.5 g/L	Interaction with bacterial genome	Q2
Dogan et al.	2011	Turkey	Oncorphydus muykiss	0.0735, 0.3675, and 0.7350 mg L^{-1}	↑lipid peroxidation, and DNA damage in liver and brain	Q1
Du et al.	2013	China	Rat	2.4, 0.5, 0.04, and 0.05 mg/kg	↑ DNA damage and oxidative stress in liver cells	Q1
Duan et al.	2017	China	Human	–	↑ telomere length and p53 and p21 expression in blood	Q1
Ellingham et al.	1986	USA	Oyster toadfish	10-2-10-5 M	↑ sister chromatid Exchange and choromosomal aberration in peripheral lymphocytes	-
Fadic et al.	2017	Chile	Tradescantia		↑ micronucleated cells in plant	Q1
Geetanjali et al.	1993	India	mice	40–400 mg/L	↑ micronucleus in bone marrow cells	Q1
Haytat et al.	2018	Pakistan	Bees	0.00–2.05 μg/g	↑ DNA damage in hemolymph by comet assay	Q1
Jamil et al.	2004	India	Human	4–10 ng/mL	↑ DNA damage in lymphocytes	Q3
Kakani et al.	2008	Greece	Bactrocera Oleae	4–150 ng/g	↑ mutations in the Acht gene	Q1
Karpeta-Kaczmarek al.	2016	Poland	Chorthippus biguttulus grasshoppers (Insecta: Orthoptera)	0.16 μg/mL	↑ DNA damage in hemocytes	Q1
Khajehali J et al.	2010	Belgium	Tetranychus urticae (Acari)	10−7 and 10−3 M	↑ mutations in the Acht gene	Q1
Kizilet et al.	2019	Turkey	Human	0.5-1-2 μg/mL	↑ micronucleated cells in lymphocytes	-

Table 1 (continued)

Author(s)	Year of publication	Country	Experimental test system	Dose	Main findings	Journal ranking (Scimago Quartile)
Kristensen et al	2006	Denmark	Musca domestica	0.14–1.4 μg/mg	↑ mutations in the Acht gene	Q1
Li et al.	2016	China	Rat	0.05–2.4 mg/kg	↑ DNA damage ↓catalase, SOD and gluthatione expression in kidney cells	Q3
Lokeshwari et al.	2016	India	Aphis gossypii Glover	131.87, 158.65, and 99.29 μmol	↑ mutations in the Acht gene	-
Mehl et al.	1994	Norway	Guinea pig	72 mb/kg	↑ DNA alkylation in brain cells	Q1
Mohammed and Ma	1999	Malasya	Tradescantia	125–501 ppm	No genotoxicity	Q1
Nehéz and Désі	1996	Hungary	Rat	7.0, 9.33, and 14.0 mg/kg	↑ chromosome aberration in bone marrow cells	Q1
Nehez et al.	1983	Hungary	Mice	60–69 mg/kg	↑ chromosome aberration in bone marrow cells	Q2
Osaba et al.	1999	Spain	Drosophila melanogaster	0–0.0050 mM	No genotoxicity	Q1
Pan et al.	2010	China	Aphys gossyppi	24–1303 mg/L	↑ mutations in the Acht gene	Q2
Qi et al.	2017	China	Rat	0.05–2.4 mg/kg b	↑ DNA damage in lymphocytes	Q2
Rehana et al.	1996	India	E. Coli	0.41–0.56 ppb	↑ mutations and interference with DNA repair system	Q1
Rehana et al.	1995	India	E. Coli	0.20–0.41 ppb	↑ mutations and interference with DNA repair system	Q1
Rong and Yin	2004	China	zebrafish	1.0 to 100 mg/L	Changes in polymorphysms	Q1
Samarawickrema et al.	2008	Sri Lanka	Human	–	↑ DNA damage and oxidative stress	Q2
Shang et al.	2014	USA	Aphis gossyppi	24–5657 mg/L	↑ mutations in the Acht gene	Q2
Sun et al.	2005	China	Aphis gossyppi	55–6116 mg/L	↑ mutations in the Acht gene	-
Undeger and Basaran	2005	Turkey	Human	10–200 mg/mL	↑ DNA damage in lymphocytes	Q1
Undeger et al.	2000	Turkey	Rat	7–28.2 mg/kg/	↑ number of chromosomes in bone marrow cells	Q1
Vontas et al.	2002	UK	Bactrocera oliae	0.03 mM	↑ mutations and interference with DNA repair system	Q1
Wang et al.	2019	China	Human	–	↑telomere length and Mutations in blood	Q1
Wilczek et al.	2016	Poland	Xerolycosa memoralis	0.16 μg/μL	↑ DNA damage in haemocytes and midgut gland cells	Q1
Woodruff et al.	1983	USA	Drosophila melanogaster	1 ppm	Negative results	-
Xamena et al.	1988	Spain	Drosophila melanogaster	0–5 ppm	Negative results	Q1
Yahia and Ali	2018	Egypt	Rat	310 mg/kg	↑ oxidative stress and DNA damage in liver and brain cells	Q2

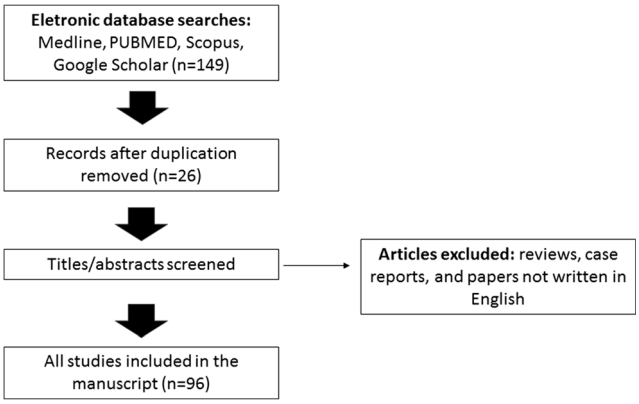

Fig. 1 Dimethoate review

and brain following dimethoate exposure (Dogan et al. 2011). The same results were obtained to guinea pigs (Mehl et al. 1994). However, this was not confirmed when rats were exposed to dimethoate evaluating the same target organs (Cunningham et al. 1994).

Other species have also been studied over mammals for identifying the genotoxicity induced by dimethoate. For example, changes in polymorphisms of some genes were detected in zebrafish exposed to dimethoate (Rong and Yin 2004). Recently, Hayat et al. (2018) have detected DNA damage in hemolymph from bees environmentally exposed to the insecticide. Following the same approach, other authors have demonstrated genetic injury in hemolymph from *Folsomia candida* in soil crops (Cardoso et al. 2017); hemocytes from *Insceta orthoptera* (Karpeta-kaczmarek et al. 2016), midgut glands from *Xerolycosa memoralis* (Wilczek et al. 2016), and African Catfish, *Clarias gariepinu*s (Amaeze et al. 2020).

Interestingly, there are many published papers confirming that dimethoate is able to induce DNA mutations resulting in the biological scenario of species resistance. These findings were confirmed by studies on changes in the DNA sequence from Acht (acethylcholine) gene polymorphisms in several organisms, such as *Aphis gossyppi* Glover (Lokeshwari et al. 2016; Shang et al. 2014; Sun et al. 2005); *Tetranuchus urticae* (Khajehali et al. 2010); *Bactrocera oleae* (Kakani et al. 2008); and *Musca domestica* (Kristensen et al. 2006). Nevertheless, this was not confirmed by others (Carletto et al. 2010).

In order to clarify if dimethoate is able to induce point mutations in close contact with genome, several studies have employed the AMES tested by means of *Escherichia coli*. In fact, the study conducted by Ansari and Malik (Ansari and Malik 2009a,b) have demonstrated positive mutagenicity and interference with DNA repair system in *E. coli* exposed to the insecticide. These results are in agreement with Aleem and Malik (2005) and Rehana et al. (1995, 1996).

In the Tradescantia plant bioassay, increased micronucleated cells were also detected after exposure to dimethoate (Fardic et al. 2017; Mohamed and Ma 1999). When the genotoxic potential of dimethoate was investigated to *Drosophila meganogaster*, conflicting results were presented. Osaba et al. (1999), Xamena et al. (1988), and Woodruff et al. (1983) failed to detect any genotoxicity in this experimental test system. It is important to stress that the studies evaluated low doses of dimethoate. Probably, this could explain the negative data found.

Oxidative stress

We found many published papers demonstrating that dimethoate is a powerful oxidant agent in mammalian cells (Fig. 1). Of particular importance, the data have revealed that the pesticide is a harmful agent in multiple tissues and organs. These findings are summarized in Table 2. For example, dimethoate produced free radicals and blocked the antioxidant defense system in erythrocytes. Rats exposed to a single low dose of dimethoate (0.01% LD[50]) caused lipid peroxidation associated with induction of superoxide dismutase and catalase activities (John et al. 2001). The authors have yet revealed inhibition of glutathione *S*-transferase and acetylcholinesterase activities in rats exposed to dimethoate (John et al. 2001). Analogous results were found by means of increase in superoxide dismutase, malondialdehyde, and catalase levels in the same cells (Ben Amara et al. 2012; Barski and Spodniewska, 2012; Abdallah et al. 2011; Gargouri et al. 2011). Membrane-bound enzymes such as Ca(2+)-ATPase and acetylcholinesterase (AChE), Na(+)-K(+)-ATPase were also inhibited after dimethoate exposure (Ben Amara et al. 2012; Pan et al. 2010; Singh et al. 2006).

When rats were exposed during 30 days to dimethoate at 0.2 g/L dose in drinking water, severe oxidative stress in lung was evidenced by increasing malondialdehyde, protein carbonyl groups, and advanced oxidation protein products (Wang et al. 2016). An increase in superoxide dismutase, glutathione peroxidase, catalase followed by decreased acetylcholinesterase and butyrylcholinesterase activities, glutathione, and non-protein thiols levels were observed as well (Wang et al. 2016).

Epididymis spermatozoa were treated for 3 h at 37 °C with increasing concentrations of dimethoate (50, 100, and 200 μm) (Ben Abdallah et al. 2012). The results showed that the insecticide caused strong oxidative damage in spermatozoa as depicted by increased malondialdehyde levels (Ben Abdallah et al. 2012) followed by increased lipid peroxidation (Astiz et al. 2019 a, b; Jallouli et al. 2016). However, a decrease in superoxide dismutase, glutathione, and catalase were detected in vivo (Jallouli et al. 2016; Ben Abdallah et al. 2012). In mice, the same results were found, because subchronic exposure to dimethoate at 20 mg/kg/day for 30 days increased lipid peroxidation and decreased the levels of antioxidant enzymes in testis (Jallouli et al. 2015).

Liver is also a potential target for dimethoate toxicity. Rats treated with dimethoate (i.p. 1/250 LD50) for three times a

Table 2 Publications regarding oxidative stress induced by dimethoate in alphabetical order

Author(s)	Year of publication	Country	Experimental test system	Dose	Main findings	Journal ranking (Scimago Quartile)
Abdallah et al.	2011	Tunisia	Human	0–100 mM	↑ malondialdehyde (MDA) levels, superoxide dismutase (SOD), and catalase (CAT) in erythrocytes	Q2
Al-Awthan et al.	2019	Saudi Arabia	Guinea Pig	14 mg/kg	↑ lipid peroxidation (LPO) ↓ catalase (CAT) and glutathione-S-transferase (GST) in liver	Q3
Al-Awthan et al.	2014	Saudi Arabia	Guinea Pig	14 mg/kg	↑ serum level of liver enzymes (AST, ALT, ALP)	Q3
Amara et al.	2013	Tunisia	Rat	0.2 g/L	↑glutathione peroxidase, superoxide dismutase, and catalase activities in heart	Q2
Astiz et al.	2009a	Argentina	Rat	15 mg/kg	↓Glutathione reductase in liver	Q1
Astiz et al.	2009b	Argentina	Rat	15 mg/kg	↑fatty acid peroxidation.	Q1
Astiz et al.	2013	Argentina	Mice	15 mg/kg	↓ glutathione and α-tocopherol levels in all brain regions	Q1
Ayed-Boussema et al.	2012b	Tunisia	Mice	1–30 mg/kg	↑ lipid peroxidation, catalase and protein carbonyl levels in the liver and kidney in a dose-dependent manner.	Q2
Bannaae et al.	2019	Iran	Galba truncatula	0–1000 μg/L	↑superoxide dismutase (SOD), glutathione S-transferaz (GST), glutathione peroxidase (GPx), catalase (CAT) and malondialdehyde (MDA), glutathione (GSH)	Q1
Barski and Spodniewska	2012	Poland	Rat	25 mg/kg	↑CAT, SOD and GPx in erythrocytes	Q2
Ben Abdallah et al.	2012	Tunisia	Rat	50–200 μm	↑ MDA levels ↓activities SOD, CAT and GPx in sperm	Q2
Ben Amara et al.	2012	Tunisia	Rat	0. g/L	↑malondialdehyde levels, superoxide dismutase and glutathione peroxidase activities in their erythocytes, ↓ catalase activities, glutathione, non-protein thiol, vitamin E and vitamin C in erythrocytes	Q2
Ben Amara et al.	2011	Tunisia	Rat	0.2 g/L	↑malondialdehyde ↓ glutathione, superoxide dismutase, catalase and non-protein thiol levels in liver	Q1
Dogan et al.	2011	Turkey	Oncorhynchus mykiss	0.0735, 0.3675, and 0.7350 mg L^{-1}	↑GPx activity and SOD activity in brain tissue.	Q1
Ferreira et al.	2015	Portugal	Porcellionides pruinosus	0.4 mg/kg	↓ acetylcholinesterase enzyme, associated with changes in the levels of GST, CAT or LPO.	Q1
Gargouri et al.	2011	Tunisia	Human	0–100 mM	↑ malondialdehyde levels, superoxide dismutase, and catalase ↓thiol in erythrocytes	Q2
Isnas et al.	2012	Turkey	Rana ridibunda	10–20 ppm	↑ MDA content ↓ GSH-Px, GST, SOD and GSH levels d	Q2
Jallouli et al.	2016	Tunisia	Rat	20 mg/kg	↑ lipid peroxidation level ↓ antioxidant enzymes (SOD and catalase) in the testis	Q2
Jallouli et al.	2015	Tunisia	Mice	20 mg/kg	↑ lipid peroxidation level ↓ antioxidant enzymes (SOD and catalase) in testis of mice	Q2
John et al.	2001	India	Rat	0.03 mg/kg	↑ catalase, superoxidade dismutase expression ↓expression of glutationes in erythrocytes	Q1
Kamath and Rajini	2007	India	Rat	20–40 mg/kg	↑ lipid peroxidation and ROS levels in the pancreatic tissue	Q1
Kim et al.	2015	South Korea	rotifer Brachionus koreanus	0.01–20 mg/L	↑ Bk-Cu/Zn-SOD in a dose-dependent manner	Q1
Kwape et al.	2013	Botswana	Rat	6 mg/kg	↑ reduced glutathione (GSH), vitamin C and E, superoxide dismutase, catalase, cholineasterase and lipid profiles	Q3

Table 2 (continued)

Author(s)	Year of publication	Country	Experimental test system	Dose	Main findings	Journal ranking (Scimago Quartile)
Li et al.	2016	China	Rat	0.05–2.4 mg/kg	↑ malondialdehyde ↓catalase, superoxide dismutase activities and glutathione levels in kidney	Q3
Mesallam et al.	2018	Egypt	Rat	20 mg/kg	↑ lipid peroxidation ↓ antioxidant system {reduced glutathione (GSH), catalase (CAT), superoxide dismutase (SOD)} activities in pancreas	Q2
Novais et al.	2014	Portugal	Enchytraeus albidus	0.5–25 mg/kg	↓ ChE	Q2
Özkol et al.	2012	Turkey	Rana ridibunda Pallas	10–20 ppm	↑MDA in lung and stomach tissues ↓GSH content fluctuated in lung and muscle; ↓GST, GR and CAT in tongue	Q2
Saafi et al.	2011	Tunisia	Rat	20 mg/kg	↑ superoxide dismutase (SOD) and glutathione peroxidase (GPx) ↓decrease catalase (CAT) activity in liver.	Q2
Saafi-Ben Salah et al.	2012	Tunisia	Rat	20 mg/kg	↑ lipid peroxidation in kidney	Q1
Serdar	2019	Turkey	Gammarus pulex	0–320 μg/L	↑MDA, GSH levels SOD, CAT, GPx, and GST activities of G. pulex	Q2
Shadegan and Banaee	2018	Iran	fish Bacilar	16–32 μg/L	↑malondialdehyde (MDA), ALP, AST, alanine aminotransferase (ALT) and CAT activity in liver and kidney	Q1
Sharma et al.	2005a	India	Rat	45, 75, and 90 mg/kg	↑ Cytochrome P450, lipid peroxidation, catalase, superoxide dismutase, glutathione peroxidase ↓ glutathione reductase in liver and brain	Q1
Sharma et al.	2005b	India	Rat	0.6, 6, and 30 mg/kg	↑ hepatic cytochrome P450, lipid peroxidation, catalase, superoxide dismutase, glutathione peroxidase, glutathione reductase in liver and brain	Q1
Singh et al.	2006	India	Rat	–	↓erythrocyte glucose-6-phosphate, dehydrogenase (G-6-PD) activity ↑ glutathione-s-transferase (GST) and glutathione reductase (GR) in erythrocytes	–
Stalmach et al.	2015	Poland	Wolf spiders Xerolycosa nemoralis	0.16 μg/1 μL	↑CAT and GSTPx and CAT	Q1
Wang et al.	2016	China	Rat	60 mg/kg	↓glutathione in the lung	Q2
Yahia and Ali	2018	Egypt	Rat	310 mg/kg	↑MDA ↓ GPx levels in brain	Q2
Yan et al.	2015	China	Mice	15 mg/kg	↑superoxide dismutase, glutathione peroxidase, catalase and lipid peroxidation products (malondialdehyde) in liver	Q1
Yang et al.	2012	China	Rat	0.5 mg/kg	↑superoxide dismutase, glutathione peroxidase, catalase and lipid peroxidation products (malondialdehyde) in liver	Q2

week during 5 weeks induced fatty acid peroxidation in hepatocytes (Astiz et al. 2009a,b). When dimethoate was administered at doses ranging from 45 to 90 mg/kg, the results revealed an increase in cytochrome P450, lipid peroxidation, superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase levels in hepatic cells at higher doses only (Sharma et al. 2005a).

In further consideration of liver, the effects of low doses of dimethoate demonstrated similar outcomes as those found to high doses. This is because dimethoate increased the levels of superoxide dismutase, cytochrome P450, lipid peroxidation, catalase, glutathione peroxidase, and reductase at doses 6, 20, and 30 mg/kg (Kwape et al. 2013; Saafi et al. 2011; Sharma et al. 2005b). Glutathione-*S*-transferase increased at 6 and 30 mg/kg doses (Sharma et al. 2005b). Others have yet demonstrated that exposure to dimethoate for 30 days at 2 g/L dose trigged oxidative stress increasing malondialdehyde levels followed by decreasing glutathione and non-protein thiol levels in rat liver. A low expression of superoxide dismutase, glutathione peroxidase, and catalase activities were also noticed in this cellular type (Ben Amara et al. 2011).

In mice treated with concentrations ranging from 1 to 30 mg/kg for 30 consecutive days, dimethoate was able to inhibit acetylcholinesterase activities in liver cells. The pesticide increased lipid peroxidation and protein carbonyl levels in a dose-dependent manner. Catalase activity increased at doses higher than 5 mg/kg (Yan et al. 2015; Ayed-Boussema et al. 2012b). It seems that results show that lipid peroxidation as well as antioxidative defense mechanisms in rodents display different responses, being dependent upon pesticide treatments and doses (Yang et al. 2012).

Other mammalian species such as guinea pig shows the same results found in rodents. Dimethoate induced a significant increase in lipid peroxidation, and decrease in the activities of catalase and glutathione-*S*-transferase in liver of guinea pigs exposed to dimethoate at 14 mg/kg during 21 days (Al-Awthan and Bahattab 2019). The insecticide also increased serum levels of hepatic marker enzymes (AST, ALT, and ALP) in guinea pig at high dose administrated (80 mg/kg) (Al-Awthan et al. 2019, 2014).

Daily administration of dimethoate (20 and 40 mg/kg b.w.) for 30 days induced elevated levels of specific markers in pancreas, as for example, amylase and lipase. Interestingly, these biochemical dysfunctions were associated with high ROS levels and lipid peroxidation in pancreas suggesting the presence of oxidative damage in this metabolic organ (Kamath and Rajini 2007). In particular, dimethoate was able to significant increase in pro-fibrotic cytokine (TGF-β1) and this is strongly associated with reduction of the antioxidant enzymes, such as reduced glutathione, catalase, and superoxide dismutase activities (Messallam et al. 2018).

In kidney, dimethoate was administered at doses of 1, 5, 10, 15, and 30 mg/kg for 30 consecutive days in BALB/c mice. The pesticide inhibited acetylcholinesterase activities in kidney of mice followed by increased lipid peroxidation and protein carbonyl levels in a dose-dependent manner (Li et al. 2016; Saafi-Ben Salah et al. 2012). A decrease in gluthatione and plasma urea levels and an increase in superoxide dismutase and catalase activities were observed (Ben Amara et al. 2013; Ayed-Boussema et al. 2012b).

In heart, female Wistar rats were exposed to dimethoate for consecutive 30 days (0.2 g L^{-1} of drinking water). The results demonstrated that the insecticide promoted oxidative stress with high levels of malondialdehyde, protein carbonyl levels, and advanced protein oxidation (Ben Amara et al. 2013). An increase of superoxide dismutase, catalase, and glutathione peroxidase activities was also detected in the heart cells of rats after dimethoate exposure (Amara et al. 2013).

Dimethoate was administered at doses 0.6, 6, and 30 mg/kg for 30 days in rats for investigating the harmful effects in brain cells. The results revealed an increase in levels of superoxide dismutase, lipid peroxidation, cytochrome P450, catalase, glutathione peroxidase, and reductase in brain cells at 6 and 30 mg/kg doses. A decrease in glutathione was observed at 30 and 6 mg/kg. Glutathione-*S*-transferase increased at 30 mg/kg dose (Yahia and Ali 2018; Sharma et al. 2005a,b).

Following the findings for brain cells, dimethoate also induced an increase in catalase, superoxide dismutase, cytochrome P450, glutathione peroxidase, lipid peroxidation, and glutathione reductase at higher doses administrated (45, 75, and 90 mg/kg) for 24 h. Likewise, there were no significant differences in glutathione and glutathione-*S*-transferase activities in these animals. Nevertheless, there was a significant increase in glutathione-*S*-transferase in brain cells at 90 mg/kg dose only (Sharma et al. 2005b). Particularly, dimethoate (i.p. 1/250 LD50) was administrated for 5 weeks causing fatty acid peroxidation (Astiz et al. 2009b). The administration of low doses of dimethoate to rats induced severe oxidative stress in some specific brain regions, such as cortex, substantia nigra, and hippocampus (Astiz et al. 2013).

In non-mammalian cells, the same results were found. Erythrocytes of *Oncorhynchus mykiss* exposed to subtheal doses of dimethoate for 5, 15, and 30 days induced an increase in glutathione peroxidase activity and high levels of superoxide dismutase in brain tissue. Lipid peroxidation increased after the exposure in both tissues and it was positively correlated with duration of exposure (Dogan et al. 2011).

In frogs, dimethoate at 10 and 20 ppm doses treated for 24, 48, 72, or 96 h, the results showed that malondialdehyde levels increased significantly in stomach and lung. Reduced glutathione was changed in muscle and lung, being increased in stomach and tongue. With respect to antioxidant enzymes (glutathione-*S*-transferase and reductase and catalase), their activities were decreased in tongue, and increased in lung (Isnas et al. 2012; Özkol et al. 2012).

The monogonont rotifer *Brachionus koreanus* transcript analysis after exposure to dimethoate indicated that the transcriptional level of Bk-Cu/Zn-SOD was increased in a dose-dependent fashion (Kim et al. 2015).

Terrestrial isopods from the species *Porcellionides pruinosus* were treated with the recommended dose application (0.4 mg/kg soil) and a sublethal concentration (10 mg/kg soil) of dimethoate. The results showed that dimethoate caused oxidative stress by inhibition of the acetylcholinesterase enzyme, associated with changes in the levels of glutathione-*S*-transferase, catalase, and lipid peroxidation. In addition, the study demonstrated that the two concentrations used of dimethoate promoted the activation of different general detoxification mechanisms (Ferreira et al. 2015). The soil organism *Enchytraeus albidus* exposed to dimethoate for 2, 4, 8, 14, and 21 days caused cholinesterase inhibition (Novais et al. 2014).

Wolf spiders *Xerolycosa nemoralis* exposed to dimethoate displayed high activity of catalase and glutathione-*S*-transferase. Moreover, exposure of individuals to dimethoate increased catalase activity, and improved reductase glutathione activity (Stalmach et al. 2015).

Acute toxicity value (LC50) in *Gammarus pulex* exposed to dimethoate demonstrated the biological competence of dimethoate for inducing oxidative stress. In particular, the results revealed that malondialdehyde, gluthationes, superoxide dismutase, and catalase were increased (Serdar 2019).

In combination with other non-heavy essential metals, such as cadmium, *Galba truncatula* exposed to 0–400 μg L^{-1} of dimethoate, and 0–1000 μg L^{-1} of cadmium chloride demonstrated that dimethoate induced oxidative stress as a result of changes in some biochemical parameters in freshwater snails such as increased levels of superoxide dismutase, glutathione-*S*-transferase, glutathione peroxidase, and catalase activities and malondialdehyde, and glutathione (GSH) levels (Bannaee et al. 2019). The association of the dimethoate and cadmium increased the effects on *Galba truncatula*. It is important to stress that dimethoate stimulated to the bioconcentration of cadmium in snails as a result of increasing oxidative stress (Bannaee et al. 2019).

The common carp, *Cyprinus carpio*, exposed to 16 and 32 μg L^{-1} of dimethoate increased aspartate aminotransferase level in gills, the activity of catalase (0.2 ml L^{-1}) in kidney, but it decreased the activity of lactate dehydrogenase and glucose 6-phsphate dehydrogenase in liver cells. Dimethoate significantly increased catalase activities in gills. Fish exposure to dimethoate decreased total antioxidant activity and glycogen levels in liver. A significant increase was detected in

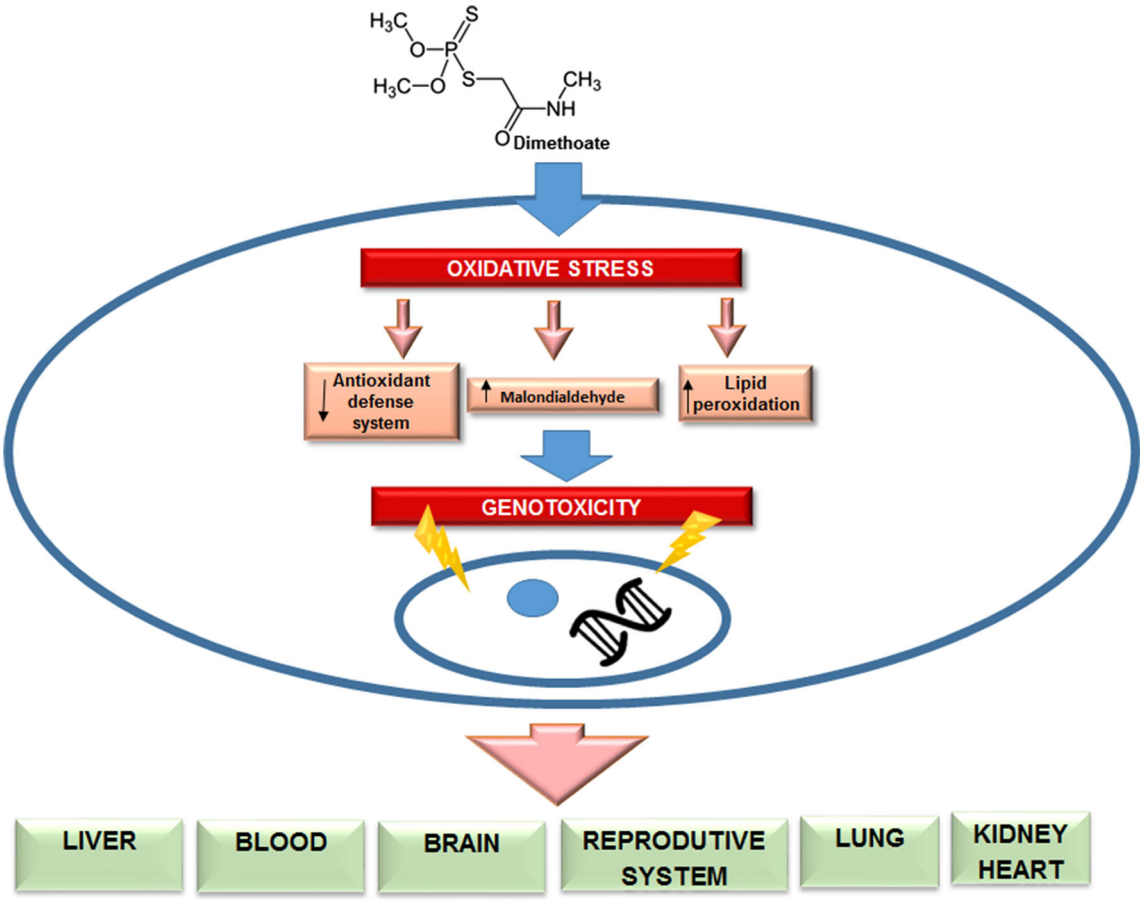

Fig. 2 Dimethoate in multiple tissues and organs

malondialdehyde and catalase activities in liver and kidney of fish exposed to dimethoate alone (Shadegan et al. 2018).

Conclusion and directions for future research

Overall, this study was able to present the current scientific knowledge on genotoxicity as a result of oxidative stress induced by dimethoate in multiple tissues and organs (Fig. 2). The approach has been documented in the literature so far, but few papers were conducted in humans. Therefore, further studies to address the risk to mammals for dimethoate are welcomed. Additionally, an analytical method for monitoring dimethoate in human body fluids is timely. This information is important to establish dose-response relationship of exposure and levels of oxidative stress and genotoxicity.

On the other hand, it is important to clarify what cells and/or tissues are more sensitive to genotoxicity induced by dimethoate as well. In particular, clarification of the gene mutation potential in vivo follow up studies to the positive mutagenic effects detected in mammalian and non-mammalian cells in vitro with dimethoate must be provided.

One of the most obvious limitations to any literature review is the quality of the available information. Since the mini-review has investigated the genotoxicity as a result of oxidative stress by dimethoate, to search other contexts and paradigms are also relevant in the context of chemical toxicity. For example, it would be interesting to know if and to what extent, dimethoate is able to interfere with cell cycle regulatory proteins in order to establish the role of apoptosis and cellular death after exposure to the insecticide. Curiously, the scientific literature was not able to conclude on the endocrine disruptor potential of dimethoate. Therefore, the interaction of dimethoate with the thyroid-signaling pathway in humans cannot be excluded. Certainly, these data play a crucial role for validating some end-points from published studies using microorganisms and rodents in so far as predict the real risk of dimethoate on carcinogenesis.

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Declarations

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Informed consent For this type of study, formal consent is not required.

Consent for publication Not applicable.

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