



Organophosphate toxicity: updates of malathion potential toxic effects in mammals and potential treatments

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Abstract

Organophosphorus insecticides toxicity is still considered a major global health problem. Malathion is one of the most commonly used organophosphates nowadays, as being considered to possess relatively low toxicity compared with other organophosphates. However, widespread use may lead to excessive exposure from multiple sources. Mechanisms of MAL toxicity include inhibition of acetylcholinesterase enzyme, change of oxidants/antioxidants balance, DNA damage, and facilitation of apoptotic cell damage. Exposure to malathion has been associated with different toxicities that nearly affect every single organ in our bodies, with CNS toxicity being the most well documented. Malathion toxic effects on liver, kidney, testis, ovaries, lung, pancreas, and blood were also reported. Moreover, malathion was considered as a genotoxic and carcinogenic chemical compound. Evidence exists for adverse effects associated with prenatal and postnatal exposure in both animals and humans. This review summarizes the toxic data available about malathion in mammals and discusses new potential therapeutic modalities, with the aim to highlight the importance of increasing awareness about its potential risk and reevaluation of the allowed daily exposure level.

Keywords Organophosphate toxicity · Pesticide toxicity · Malathion · Malathion pharmacokinetics · Malathion pharmacodynamics · Malathion toxicity

Introduction

In the past decades, the pesticides were utilized to enhance agricultural productivity and minimize losses by controlling unwanted insects, worms, and animals, in addition to eradicating disease vectors in different parts of the world (Bhardwaj and Saraf 2014). However, they are not totally beneficial; they are important sources of environmental pollution and exert adverse health consequences, some of which are irreversible (LaVerda et al. 2015; Navarrete-Meneses et al. 2017). Pesticides induce both acute and chronic toxic effects including neurological manifestations, respiratory diseases, genetic damage, and reproductive disorders in various organisms (Bhardwaj and Saraf 2014; Bhardwaj et al. 2018).

Pesticide poisoning is being considered as an important cause of morbidity and mortality, especially in developing countries. Nevertheless, every year there are three million cases of acute poisoning and 220,000 deaths; the majority of these poisoning and 49% of the resulting death occur in third world countries (Seth et al. 2001).

Organophosphate synthetic pesticides (OPs) are being widely used since the mid-1940s for controlling pest (Ozsoy et al. 2016; Esen and Uysal 2018). They are highly toxic to humans and are considered potential hazards to human health (El-Bini Dhouib et al. 2015). Epidemiological studies investigated the relationship between a high level of OP exposure and adverse health effects (Navarrete-Meneses et al. 2017). They act by inhibiting acetylcholinesterase (AChE), an enzyme hydrolyzing acetylcholine in cholinergic synapses and neuromuscular junctions, by phosphorylating it. They are thus called AChE inhibitors (El-Bini Dhouib et al. 2015). Inhibition of AChE causes accumulation of acetylcholine, with subsequent increased activity of cholinergic muscarinic, in addition to nicotinic receptors (Velmurugan et al. 2017; Esen and Uysal 2018). Despite anticholinergic treatment and sophisticated intensive care facilities, severe OP poisoning has a high mortality rate (~25–40%) (Kang et al. 2009).

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Therefore, a better understanding of the pathophysiology caused by OPs and the development of new treatment modalities are of great importance in OP toxicity (Esen and Uysal 2018; Vanova et al. 2018).

Malathion

Malathion (MAL) (S-(1,2-dicarbethoxyethyl) O,O-dimethyl dithiophosphate) (Fig. 1), is being used, since 1980, in agriculture, industry, and veterinary medicine. As MAL is considered to have relatively lower acute toxicity as compared with other OPs, it is now one of the most extensively used pesticides (Ozsoy et al. 2016; Bogen and Singhal 2017). Even though commonly named as a pesticide, it is still used therapeutically for pediculosis (Varol et al. 2015). This widespread use leads to environmental pollution and increases the extent of exposure, and almost any individual may be exposed to MAL through different routes (dos Santos et al. 2016; Navarrete-Meneses et al. 2017). Moreover, traces of MAL have been detected in the blood, urine, and hair of pregnant women (Bossi et al. 2013; Navarrete-Meneses et al. 2017). Thus, OPs, including MAL, remain a serious health hazard.

MAL exposure may cause subacute, acute, or chronic toxicity, and both incidental and intentional MAL toxicity were recorded especially in developing countries (Varol et al. 2015). Occupational and nonoccupational exposures to MAL have been reported in adults and children (Eskenazi et al. 2007; Salvatore et al. 2008; Fenske et al. 2013; Voorhees et al. 2016; Smith et al. 2017). Workers of MAL manufactories, people who work in agriculture and their families, those living near farms, and those performing the home application of pesticides or eating food highly contaminated with pesticides are highly susceptible to MAL intoxication (Jaga and Dharmani 2003; Waheed et al. 2017). MAL toxicity is mainly caused by its metabolites and is affected by different variables including product purity (as contaminants may aggravate MAL toxicity), route of exposure, nutritional status, genetics, and gender (Moore et al. 2011).

Malathion pharmacokinetics and pharmacodynamics

MAL may represent a greater risk than it would be expected. The toxicity of malathion is highly correlated with its metabolites and affected by MAL contaminants (Baiomy et al.

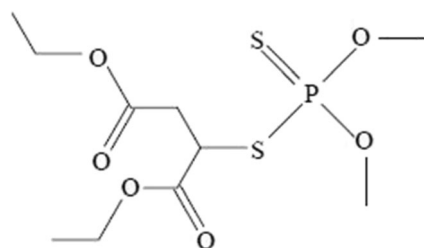


Fig. 1 Chemical structure of malathion (Naughton and Terry 2018)

2015). Therefore, with the aim to understand MAL toxicity, we first have to understand the pharmacokinetics of MAL, as well as its pharmacodynamics.

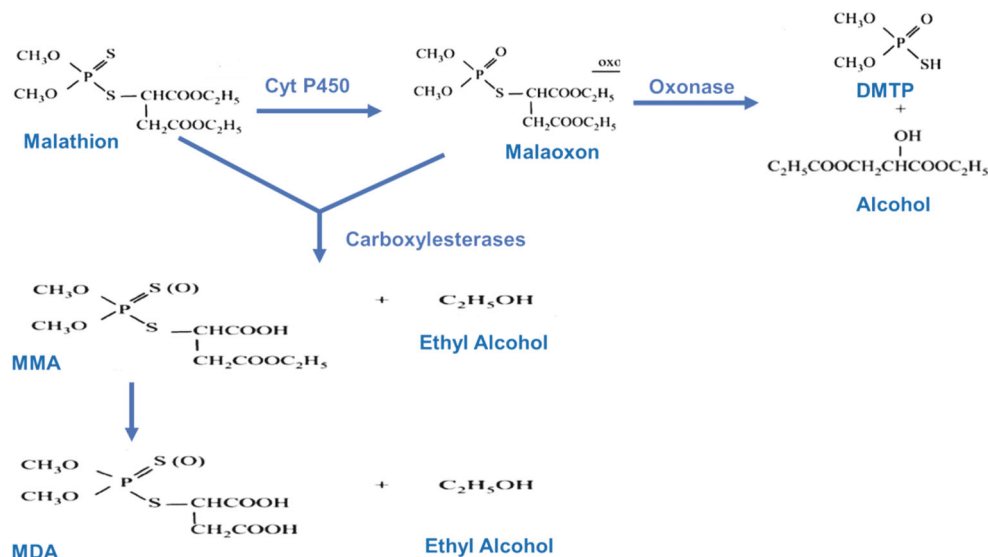
Pharmacokinetics of malathion

Mammals can be adversely affected by MAL through nearly any route of exposure, including the oral ingestion of food and drinking water contaminated with MAL (Sapbamrer and Hongsibsong 2014; Akbel et al. 2018), dermal absorption (Geng et al. 2015b), conjunctival (Kamanyire and Karalliedde 2004), and respiratory exposure through occupational or nonoccupational during contact with contaminated soil and plants, working at pesticides factories, handling and applying of MAL, or from accidental spills (Machera et al. 2003; Ozsoy et al. 2016). Acute MAL toxicity occurs mostly orally (Esen and Uysal 2018); however, the major route of occupational exposure is the dermal one (Tchounwou et al. 2015).

Generally, OPs are relatively rapidly absorbed, metabolized, and excreted in the form of more hydrophilic metabolites in both animals and humans (Chambers and Levi 2013). Similarly, due to its lipophilic nature, MAL is rapidly absorbed, through different routes, and distributed to different body organs, thus leads to several pathologies (Selmi et al. 2018). Like other OPs, MAL requires cytochrome P-450-mediated metabolic activation for cholinergic toxicity (Abdollahi et al. 2004). It is metabolized through desulfuration to an active metabolite, malaoxon, that strongly inhibits AChE (Guyton et al. 2015) (Fig. 2). At low MAL concentration, malaoxon formation is catalyzed by CYP1A2 and 2B6 (to a lesser extent); however, 3A4 plays a relevant role only at high MAL concentrations (Buratti et al. 2005). The metabolites, produced by MAL oxidation, are considered the primary source of its toxicity and malaoxon is found to be 40 times more toxic than MAL (Baiomy et al. 2015).

On the other hand, MAL and malaoxon can be rapidly and effectively detoxified by carboxylesterases to form monocarboxylic acid (MMA), which also competes with malaoxon for the cytochrome P-450s (Fig. 2) (Buratti and Testai 2005; Chen et al. 2013). Carboxylesterases are widely distributed in mammalian tissue, with the highest levels exist in the liver, the gastrointestinal tract, and the brain (Brodeur and DuBois 1967; Buratti and Testai 2005). However, some contaminants of commercial MAL formulations are potent inhibitors of carboxylesterase, thus shifting the balance toward a significant increase in malaoxon formation; this may explain the role of contaminants in aggravating MAL toxicity (Buratti et al. 2005). In 1976, an epidemic of MAL poisonings occurred in Pakistan, emphasizing the role of impurities in the commercial formulations. Actually, at a level of exposure, which should not produce adverse effects on humans, about 2800 workers (spraymen and mixer operators) suffered from variable

Fig. 2 Major pathways of MAL metabolism. Figure modified from that of Buratti and Testai (2005). DMPT dimethylthiophosphate, MMA malathion (malaoxon)-monocarboxylic acid, MDA malathion (malaoxon)-dicarboxylic acid



degrees of toxicity and five died (Hosokawa et al. 1990). The unexplained toxicity was related to isomalathion contaminant that inhibits carboxylesterases, with subsequently increased malaoxon formation (Hosokawa et al. 1995; Josse et al. 2014).

Regarding excretion, MAL and its metabolites have relatively low accumulation potential and are excreted primarily by the kidney, followed by the lung and the intestinal route (Waldron Lechner and Abdel-Rahman 1986; Tchounwou et al. 2015). The metabolites excreted in the urine can be convenient biomarkers of occupational exposure since they represent an internal or absorbed dose and they require only few measurements to reliably estimate workers' exposure (Ross et al. 2008). MAL is also excreted in breast milk and can inhibit AChE of the offspring and thus was associated with various psychological and biological outcomes in exposed offspring (da Silva et al. 2006).

Pharmacodynamics of malathion

Acute, subchronic and chronic toxicity reports concluded that MAL is toxic to mammals (Wang et al. 2014; Ozsoy et al. 2016). It has toxic effects on experimental animals and exposed workers. MAL exposure was correlated with the dysfunction of several organs, including the liver, kidney, pancreas, testis, and brain (Ozsoy et al. 2016; Esen and Uysal 2018). MAL can also lead to metabolic disorders (Esen and Uysal 2018). Toxic mechanisms include inhibition of AChE, oxidative stress, induction of inflammatory response, promotion of apoptosis, genotoxicity, and immunomodulation (Nicholas et al. 1979; Geng et al. 2015b; Guyton et al. 2015; Ince et al. 2017). Toxicity depends on many factors including the level and duration of exposure, the route of exposure, age, and health status (Rosas and Eskenazi 2008; Sánchez-Santed et al. 2016).

The main mechanism of MAL toxic effects is the inhibition of AChE (Esen and Uysal 2018), with subsequent accumulation of acetylcholine, leading to excessive stimulation of both muscarinic and nicotinic receptors in the muscles and nerves of either the central, peripheral, or autonomic nervous system, evoking a wide array of cholinergic toxic manifestations (Mileson et al. 1998; Sapbamrer and Hongsihsong 2019). Acute toxicity signs and symptoms may include salivation, lacrimation, urination, and defecation (the SLUD syndrome), dyspnea, vomiting, bradycardia, abdominal pain, pinpoint pupil, and anorexia, which are caused by acetylcholine over excitation of the muscarinic receptors. Other signs of toxicity include muscle weakness, tremors, and rigidity, convulsions, and paralysis are induced as a result of acetylcholine excessive stimulation of nicotinic receptors. Finally, respiratory depression may take place, which characterizes the "cholinergic syndrome" (Kwong 2002; Takahashi and Hashizume 2014).

AChE inhibition alone cannot explain the wide range of toxic effects that were correlated with MAL exposure. Recently, oxidative stress has been proposed as the key player in accounting for both acute and chronic MAL toxic effects. Due to its lipophilic nature, MAL directly interacts with the phospholipid bilayer of cellular membranes, which causes disturbances in their structure and induces the production of free radicals (Ozsoy et al. 2016). This was experimentally studied by Rieger et al., who used pralidoxime, an AChE reactivator, to protect against cytotoxic effects of MAL in rat cortical cells. They found that pralidoxime significantly protected against MAL-induced AChE blockade; however, pralidoxime did not affect MAL-induced decrease in cellular viability, indicating that other mechanisms contribute to MAL toxic effects. They also found that MAL-induced cell death was directly linked to the increase in superoxide anion production and that antioxidant substance like ascorbic acid

significantly counteracted the decrease of cell viability with no effect on AChE activity. This provides evidence of the role of oxidative stress in MAL-induced toxicity (Rieger et al. 2017).

Many other *in vivo* and *in vitro* studies in animals supported the oxidative stress theory (Moridi et al. 2018; Arab et al. 2018); MAL-induced oxidative stress was also recently observed in many types of human cells (Durak et al. 2009; Tuzcu et al. 2014; Yan et al. 2019; Shieh et al. 2019). They found that MAL treatment leads to enhanced production of reactive oxygen species (ROS) and subsequent lipid peroxidation (Durak et al. 2009; Bhardwaj et al. 2018). It is evident that lipid peroxidation is accompanied by an alteration, either inhibition or activation, of the antioxidant defense system in different organs (Flehi-Slim et al. 2015). Different studies revealed that MAL decreased the activity of cellular antioxidant defenses, superoxide dismutase (SOD), reduced glutathione (GSH), and glutathione peroxidase (GPx), thus disrupting the oxidant-antioxidant balance in the body (Akhgari et al. 2003; Franco et al. 2009; Ozsoy et al. 2016; Ullah et al. 2018; Thakur et al. 2018). Other studies showed that the activities of antioxidant enzymes were induced by MAL as a compensatory protective mechanism (El-Bini Dhoub et al. 2015).

ROS directly or indirectly adversely affects cell membrane integrity and may even cause failure in mitochondrial function (Fortunato et al. 2006; Said et al. 2014). They can also cause oxidation of cellular molecules: lipids, proteins, and DNA (Cooke et al. 2003). DNA damage may lead to the activation of the apoptotic factors or being a putative source of genetic neoplastic mutations (Syng-Ai et al. 2004; Fouad et al. 2019). Accordingly, upregulation of apoptotic markers was also reported in association with MAL toxicity in different tissues (Masoud et al. 2003; dos Santos et al. 2016). ROS can also damage DNA leading genotoxic mutagenic and carcinogenic effects (Bagchi et al. 1995; Ojha et al. 2013). Oxidative stress-induced cell damage caused by MAL exposure affects many tissues including liver, kidney, pancreas, erythrocytes, and brain (Durak et al. 2009; Selmi et al. 2012, 2015; Tuzcu et al. 2014; Ullah et al. 2018; Shieh et al. 2019). Other mechanisms of MAL-induced toxicity were discussed later.

Toxic effects of malathion in mammals

Neurotoxicity

Many studies document the correlation between high-level OP exposure and neurological or neuropsychological impairments (Naughton and Terry 2018; Glass et al. 2018). Neurological and psychological effects of OPs can be associated with either acute or chronic exposure and may include motor dysfunction and extrapyramidal symptoms, psychosis,

anxiety, depression, as well as defects in attention, memory, problem-solving, cognition, and delayed polyneuropathy (Pereira et al. 2014; Naughton and Terry 2018). In cases of chronic toxicity, these symptoms are referred to collectively as chronic OP-induced neuropsychiatric disorders (COPIND) (Singh and Sharma 2000; Naughton and Terry 2018). Moreover, OP exposure has also been linked to the pathogenesis of neurodegenerative disorders like Parkinson's disease and Alzheimer's disease (Belin et al. 2012; Mohammadzadeh et al. 2020). Additionally, there is great evidence that suggests that prenatal and early postnatal exposure to OPs is implicated in the development of neurodevelopmental disorders in various stages, including behavioral abnormalities and deficits in attention, learning, and memory (Sapbamrer and Hongsibsong 2019).

Among mostly used pesticides, MAL is ranked fourth in targeting the nervous system (Bhardwaj et al. 2018). Manuscripts reported that it may have neurotoxic effects in both animals and humans that include a wide variety of neuromotoric, cholinergic, affective, and cognitive disorders, in addition to impairment of memory and discrimination (Komori et al. 1991; Abdel-Rahman et al. 2004; Brocardo et al. 2005; dos Santos et al. 2016). Rats treated with MAL showed neuronal degeneration in the cortex and the hippocampus that is associated with a significant decrease in the density of viable neurons in different brain regions (Sánchez-Santed et al. 2016; Abdel-Salam et al. 2017). This may be directly related to MAL-induced depressive and Parkinsonian-like behaviors (Saeedi Saravi et al. 2016; Mohammadzadeh et al. 2018). Moreover, MAL toxicity can cause muscle weakness and easy fatigability, which are associated with damage to the nervous system and the brain (Karami-Mohajeri et al. 2014; Rezg et al. 2015).

Mechanisms of malathion-induced neurotoxicity

OPs including MAL are known to modulate the expression and activity of hundreds of enzymes and proteins that may be especially relevant to the COPIND and developmental neurotoxicity. In addition to AChE inhibition, MAL-induced neurotoxicity may involve various additional non-cholinergic mechanisms including oxidative stress, neuroinflammation, axonal transport malfunctions, and apoptosis (Sánchez-Santed et al. 2016; Abdel-Salam et al. 2017) (Fig. 3).

Inhibition of AChE MAL-induced neurotoxicity can be explained in terms of increased acetylcholine following AChE inhibition (Kwong 2002). This is especially important in cases of acute MAL toxicity. However, it is worthy to note that COPIND does not appear to be dependent on AChE inhibition alone (Naughton and Terry 2018). It was also found that MAL affects brain AChE rats and mice pups exposed during lactation (da Silva et al. 2006; Selmi et al. 2012). Although AChE

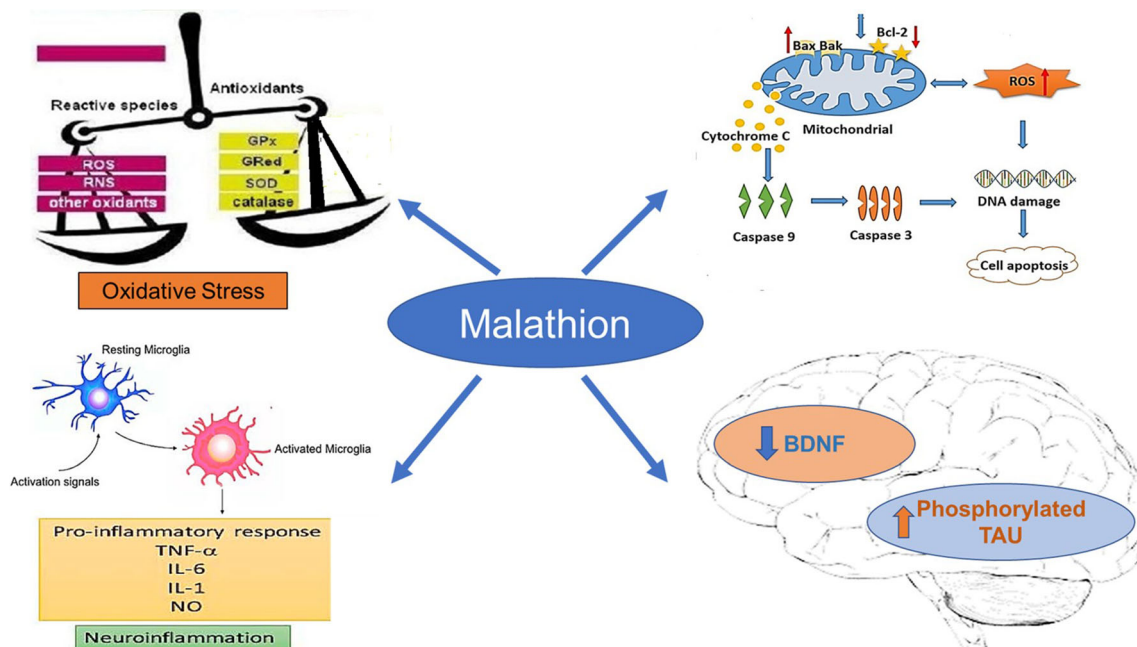


Fig. 3 Non-cholinergic mechanism of malathion-induced neurotoxicity. Malathion induces oxidative stress by unbalancing oxidants: reactive oxygen species (ROS), reactive nitrogen species (RNS), and others; and antioxidants: glutathione peroxidase (GPx), glutathione reductase (GRed), superoxide dismutase (SOD), and catalase. Malathion can also activate microglia to release inflammatory mediators: tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), IL-6, and nitric oxide (NO); and

induce neuroinflammation. ROS can induce apoptotic pathways by inducing mitochondrial damage, with subsequent increased Bax/Bcl-2 ratio, release of cytochrome C, and the resultant activation of lethal caspase-3. ROS and caspases can induce DNA breaks and damage. Other postulated mechanisms include increased phosphorylation of TAU and reduced level of brain-derived neurotrophic factor (BDNF)

inhibition certainly plays a key role in MAL-induced neurotoxicity, but when alone cannot explain the wide range of neurological signs and symptoms that have been reported (Venkatesan et al. 2017). Therefore, different non-cholinergic mechanisms have been proposed.

Oxidative stress and inflammation Unlikely, the brain has the propensity to suffer a significant oxidative injury due to its lipid composition, which is easily oxidized due to its high oxygen consumption rate and relatively low concentration of antioxidant substances. As induction of oxidative stress plays an important role in MAL toxic effects, MAL-induced oxidative stress appears to be directly correlated to MAL-associated neurotoxicity. This was emphasized by the consistent MAL-induced alterations in endogenous enzymatic and nonenzymatic antioxidant activities in brain tissues that was associated with subsequent disruption in mitochondrial functions and enhanced incidence of free radical-mediated injury such as lipid peroxidation (Fortunato et al. 2006; Abdel-Salam et al. 2017). MAL increased oxidative stress markers, total oxidative status, and malondialdehyde (MDA) levels and reduced activity of antioxidant protective machinery, total antioxidant capacity (TAC), and SOD in brains of MAL-treated groups compared with that of the control group (Fortunato et al. 2006;

Yu et al. 2013; Varol et al. 2015; Mohammadzadeh et al. 2020) (Fig. 3). Mohammadzadeh et al. (2018) found that subchronic MAL exposure induced Parkinsonian-like behavior with oxidative stress being considered to play an important role in its development (Mohammadzadeh et al. 2018).

MAL-induced oxidative stress in the brain was reported to be mediated through increased endogenous nitric oxide (NO) biosynthesis and inducible NO synthase (iNOS) expression in the rat brain. This was concluded when neuronal damage was minimized by the use of a nonselective NOS antagonist, (L-NAME), and the selective neuronal NOS antagonist, 7-NI (Abdel-Salam et al. 2017). A further contributor to MAL-induced neurotoxicity is the Paraoxonase enzyme (PON-1), an enzyme of marked interest in the view of its ability to modulate OP toxicity. PON-1 possesses arylesterase and lactonase activities and thus hydrolyzes the active metabolites of many OPs, including MAL (Primo-Parmo et al. 1996; Hosseini et al. 2019). The antioxidant and anti-inflammatory properties of PON-1 has also been proposed (Lou-Bonafonte et al. 2015). Sufficient evidence has revealed that serum PON-1 activity can be inhibited by OPs (Costa et al. 2005). Thus, this may decrease the protective ability of PON-1 against free radicals (Shih et al. 1998). A

decrease in PON-1 activity in rat brain exposed to MAL was found, and the effect was dose-dependent (Varol et al. 2015; Abdel-Salam et al. 2017).

Santos et al. (2012) proposed a potential link between AChE activity and oxidative stress in experimental models of neurotoxicity (Santos et al. 2012). However, Rieger et al. (2017) proved experimentally that MAL-induced oxidative stress in cortical cell culture does not involve AChE inhibition. They found that MAL-induced decreased cell viability was directly correlated with a significant increase in superoxide anion production and that the use of an antioxidant significantly protected against MAL-induced cytotoxic effects and proceeded with the decrease in superoxide anion level; however, it did not affect MAL-induced AChE inhibition. Thus, they provided a good evidence of the significant role of oxidative stress in MAL-induced neurotoxicity (Rieger et al. 2017).

On the other hand, some studies have indicated that the activities of antioxidant enzymes are unchanged in the brains of animals treated with MAL (da Silva et al. 2006; dos Santos et al. 2011). The differences found may be related to the dose and duration of MAL exposure that were employed (Brocardo et al. 2005).

Neuroinflammation also plays a role in neurotoxicity induced by OPs. The proinflammatory cytokines play a magnificent role in mediating neuronal damage (Banks and Lein 2012). Oxidative stress and inflammation are usually interconnected, and chronic oxidative stress is usually connected with inflammation. In parallel to oxidative stress, MAL induced increase in inflammatory cytokines TNF- α and IL-6 in rat brains (Mohammadzadeh et al. 2020). Chronic exposure to MAL in mice was also associated with increased microglial cell count in parallel with increased microglial activation (Ahmed et al. 2017; Naughton and Terry 2018). Microglia are brain macrophages that protects the brain and release inflammatory mediators when activated by noxious stimulus. The role of neuroinflammation was further supported by the ameliorative role of anti-inflammatory drugs against MAL-induced behavioral changes and dopaminergic neurons loss (Ahmed et al. 2017; Naughton and Terry 2018) (Fig. 3).

Mitochondrial dysfunction, DNA damage, and apoptosis

MAL-induced oxidative stress can induce mitochondrial dysfunction, DNA breaks, autophagy, and finally apoptosis (dos Santos et al. 2016). MAL-increased $O_2^{\cdot-}$ formation in sub-mitochondrial particles in the hippocampus was associated with the inhibition of mitochondrial complex I, II, and IV activities, which would have major effects on cellular energy production and may further induce oxidant-antioxidant imbalance (Delgado et al. 2006; Karami-Mohajeri et al. 2014). Defective mitochondrial function is reported to be closely related to Parkinsonism (Binukumar et al. 2010) and Alzheimer's disease (Reddy and Beal 2008). Moreover,

MAL was also found to induce DNA damage of cerebral tissues (Réus et al. 2008).

Both, mitochondrial disturbances and DNA damage may lead to the activation of apoptotic pathways. MAL treatment was found to increase proapoptotic and apoptotic proteins in the brain (Brocardo et al. 2005), such as Bax, Bak (dos Santos et al. 2016), and caspase-3 (Varol et al. 2015; Salama et al. 2019), and reduce antiapoptotic proteins, such as Bcl-2 and p-Akt (Venkatesan et al. 2017). Imbalance of proapoptotic and antiapoptotic proteins stimulates the mitochondrial release of cytochrome c and induction of caspase-dependent DNA fragmentation. MAL also induced autophagy and lysosomal membrane permeabilization in neuroblastoma cells. Lysosomal membrane permeabilization induces cathepsin B release, which may intensify apoptotic insults via its proteolytic effect (Venkatesan et al. 2017). The effect of mitochondrial disturbance and apoptosis was supported by Dos Santos et al. who showed that chronic malathion exposure, at a dose that does not inhibit AChE, induced spatial memory impairment and discrimination in mice and that the effects were correlated to mitochondrial dysfunctional and apoptosis (dos Santos et al. 2016) (Fig. 3).

Other possible mechanisms of MAL-induced neurotoxicity

MAL was also reported to induce TAU hyperphosphorylation at multiple Alzheimer disease-related sites, via activation of glycogen synthase kinase-3 β and inhibition of protein phosphatase-2A; this may support the role of MAL in Alzheimer's pathogenesis (Mohammadzadeh et al. 2020). Moreover, MAL was found to inhibit brain-derived neurotrophic factor, which plays a magnificent role in cognitive behaviors and its inhibition plays a crucial role in the development of depressive symptoms (Dorri et al. 2015) (Fig. 3).

Other mechanisms may be involved in MAL-induced neurotoxicity. Some are reported with other OPs; however, it was not clearly studied with MAL. One of these is the impairment of axonal transport by alteration of motor proteins, e.g., kinesin, or neuronal cytoskeleton proteins, such as microtubules (Naughton and Terry 2018). Another possible mechanism may involve the induction of autoimmune response in some individuals; some evidence do exist that such mechanism plays a role in other OP neurotoxic effects (El Rahman et al. 2018).

More studies are still needed to explore different mechanisms of MAL-induced neurotoxicity, with the aim to identify effective measures that help to protect high-risk populations.

Neurotoxic dose of MAL

The neurotoxic dose of MAL in humans is not specified, only data is available about MAL neurotoxic dose was collected from studies in experimental animals. Acutely, MAL induced

oxidative stress in rat brain at a dose as low as 25 mg/kg (Fortunato et al. 2006). Chronically, MAL induced cerebral oxidative stress and increased caspase-3 at very small doses (5 and 10 mg/kg daily for 28 days), and the effect was dose-dependent (Varol et al. 2015). Additionally, Abdel-Rahman et al. showed that MAL also induced neurobehavioral changes and neuronal loss after subacute dermal exposure (44 mg/kg, for 30 days) (Abdel-Rahman et al. 2004). Other experimental studies used higher doses of MAL (ranging from 35 to 100 mg/kg), either daily or every other day for about 2–4 weeks or more (Coban et al. 2015; Saeedi Saravi et al. 2016).

Malathion-induced hepatotoxicity

The liver is one of the important organs that are affected by MAL toxicity. MAL causes hepatocellular damage in liver tissue and increases the activity of liver enzymes. MAL hepatotoxicity was even reported in rat pups exposed to MAL through lactation (Selmi et al. 2015). Histopathologically, MAL treatment induces hepatic degenerative changes in the form of necrosis, congestion of the central vein, hemorrhage, and focal areas of leucocytic infiltration (Abdel-Salam et al. 2017). As expected, the decrease of AChE in the liver was reported (Ince et al. 2017). In homology with cerebral effects of MAL, several studies also documented that MAL-induced changes in oxidant-antioxidant balance in hepatic tissue, and it was believed that the affection of liver tissues caused by MAL exposure is mainly a function of the overall balance between the degree of oxidative stress and the antioxidant capacity (Baiomy et al. 2015). MAL exposure resulted in the reduction of hepatic GSH, TAC, SOD, and catalase and increment of lipid peroxidation (Lasram et al. 2014a; Selmi et al. 2015). Abdel-Salam et al. found that MAL increases NO production and induces iNOS in the liver, and thus the use of NOS inhibitors minimize MAL-induced hepatotoxicity (Abdel-Salam et al. 2017).

ROS production might cause cell damage by failure in mitochondrial function due to an increase in membrane permeability and disturbance in mitochondrial function, which consequently triggers apoptotic cell death (Ranjbar et al. 2010). Esen and Uysal found increased apoptotic proteins, Bax and caspase-3, in liver tissues exposed to MAL (Esen and Uysal 2018). In addition to the oxidative damage, the inhibition of mitochondrial respiratory complexes by OPs may also be an additional intrinsic factor that triggers apoptosis (Delgado et al. 2006; Karami-Mohajeri et al. 2014). The mitochondrial injury results in a damaged oxidative pathway, and this situation may increase the use of glucose by the way of glycolysis (Karami-Mohajeri and Abdollahi 2011).

Another possible mechanism of MAL-induced hepatocellular injury leads to inflammation and the activation of the innate immune system (El-Bini Dhoub et al. 2015). Dhoub

et al. reported increased total white blood cells (WBC) following MAL administration (9). WBCs are an essential part of the innate immunity, and their increase seems to concern particularly neutrophils and could result from an inflammation caused by MAL toxicity (Lasram et al. 2014b, a). The inflammatory response was associated with increased inflammatory cytokines production, as MAL increased hepatic expression of interferon- γ , interleukin (IL) 1- β , tumor necrosis factor- α , and nuclear factor- κ B (NF- κ B) in rats (Ince et al. 2017). Inflammatory mediators play a significant role in hepatic injury and activation of stellate cells, with a wide spectrum of hepatic damage including steatohepatitis and apoptosis (Fujii and Kawada 2012; Lasram et al. 2014a) (Fig. 4).

MAL exposure can also affect the metabolic functions of the liver. Dhoub et al. and Selmi et al. reported reduced albumin levels in rats treated with MAL and suggested the possibility of the alteration of protein and free amino acid metabolism and their synthesis in the liver by MAL (Akbel et al. 2018; Fenske et al. 2013). Moreover, MAL exposure has been also associated with altered glucose and metabolic syndromes by inducing hepatosteatosis (Lasram et al. 2009, 2014a) (Fig. 4). This may be partially caused by changes in glucose, protein, and lipid metabolism in association with MAL exposure (Wang et al. 2014). MAL induced changes of lipid metabolism; it increased total cholesterol, low-density lipoprotein-cholesterol, and triglycerides and reduced high-density lipoprotein-cholesterol; thus, MAL exposure may be related to increased risk of atherosclerosis (Selmi et al. 2015).

Changes of glucose metabolism was evident by documents reporting a strong correlation between both blood glucose level and insulin resistance and MAL blood concentration (Pournourmohammadi et al. 2007; Lasram et al. 2008; Raafat et al. 2012; Ramirez-Vargas et al. 2018), and thus

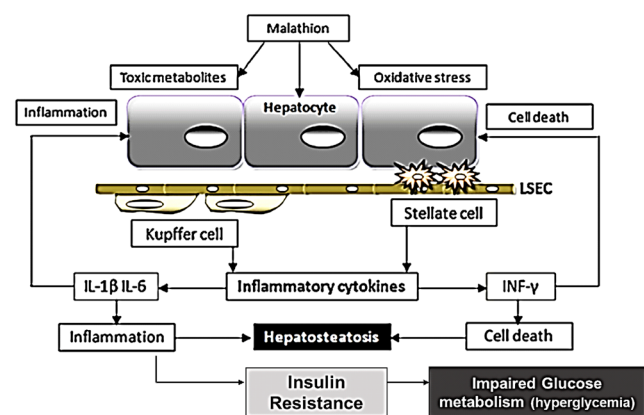


Fig. 4 Mechanisms of malathion-induced hepatotoxicity. MAL acts on hepatocytes, inducing cell damage and oxidative stress. Tissue damage stimulates hepatic Kupffer cells to release inflammatory cytokines, IL-1 β , IL-6, and INF- γ . Inflammatory cytokines affect the function of hepatocytes and stellate cells, leading to various hepatic damaging effects, e.g., hepatitis, steatosis, or apoptotic cell death. Figure adapted and modified from Lasram et al. (2014a)

OPs have been considered as potential diabetogenic (Lassiter et al. 2008; Lasram et al. 2009). MAL-induced hyperglycemia may be mediated via activation of hepatic glycogenolysis and gluconeogenesis. MAL-induced hyperglycemia can be also explained in terms of its hepatic toxic inflammatory effects (Aboul-Soud et al. 2011; Al-Othman et al. 2012). There is actually increasing evidence of the role of chronic inflammation, especially increased hepatic IKK and NF- κ B, in the development of insulin resistance (Cai et al. 2005). Thus, MAL has a considerable significant effect on hepatic pathogenesis.

Malathion-induced nephrotoxicity

The kidney is one of the target organs that are attacked by OP compounds' toxicity. MAL-treated rats showed upregulation of renal function tests, serum creatinine, urea, and uric acid (Zidan 2015; Selmi et al. 2015). Histopathologically, MAL treatment induced renal degenerative changes including cloudy swelling and cellular desquamations, as well as swollen and pleomorphic mitochondria (Keadtisuke et al. 1989; Al-Attar 2010). It was also found that MAL induces an oxidative stress status in the renal tissues, which mostly accounts for increased lipid peroxidation and depletion of GSH, GPx, catalase, and SOD (Baiomy et al. 2015; Coban et al. 2015; Yokota et al. 2017; Selmi et al. 2018).

Recently, Yokota et al. 2017 reported a case of acute renal injury and nephrotic syndrome in a man 15 days after MAL inhalation, associated with proteinuria, abnormality in serum creatinine, and glomerular and tubular damage. Recovery took about 6 weeks under steroid therapy (Yokota et al. 2017). A similar case report of acute renal failure associated with MAL inhalation was previously reported by Albright et al. (1983). These cases represent an evidence of MAL nephrotoxicity in humans and the need to be included in the differential diagnosis of nephrotoxicity.

Effects of malathion on endocrine system

Many OPs, including MAL, have been identified as endocrine disruptors, which can disturb hormone levels through different mechanisms including inhibition of hormonal secretion (MAL was found to inhibit secretion of catecholamine) or binding to and activation of hormonal receptors, e.g., thyroid hormone, estrogen, and androgen receptors (Ishihara et al. 2003; Mnif et al. 2011; Geng et al. 2015b; Schang et al. 2016).

Effects of malathion on reproductive systems

Pesticides are known to induce reproductive toxicity in animals and humans, and many studies have documented the role of pesticides in mediating infertility (Runkle et al. 2017; Sifakis et al. 2017). The adverse effects of pesticides and OPs were reported to affect the reproductive system of both

males and females (Mehrpour et al. 2014; Messerlian et al. 2018).

Effects of malathion on male reproductive system

Toxicological studies suggest that excessive use of MAL causes serious harmful effects on the male reproductive system and reduces male fertility. Choudhary et al. (2008) reported that MAL-treated experimental animals exhibited a significant decrease in the weight of the testis, seminal vesicle, epididymis, and prostate, in addition to diminished testicular and epididymal sperm count, and decreased values of fertility test by about 80% (Choudhary et al. 2008). This was supported by several studies reporting reduced motility and number of sperms and increased sperm abnormality in response to MAL treatment (Akbarsha et al. 2000; Giri et al. 2002; Geng et al. 2016; Jamal et al. 2016). Similar results were reported in adolescent male mice treated with MAL (500 mg/kg for 3 days) at the pubertal age (Slimen et al. 2014).

Histopathologically, MAL induced degenerative changes, necrosis, and edema in the interstitial tissues and seminiferous tubules (Uzun et al. 2009). In vitro effects of MAL treatment, using spermatogonial cells, showed a significant reduction of testicular germ cells viability, with histopathological changes like pyknosis, vacuolization, empty spaces, tubular degeneration, and condensed or fragmented chromatin (Bhardwaj et al. 2018). Biochemical tests were also affected, showing a significant decrease in testicular content of glycogen and sialic acid, in addition to a significant increase in testicular protein and cholesterol. The enzymatic profile was also modified, with increased activity of lactate dehydrogenase and testicular acid phosphatase, and reduced activity of testicular alkaline phosphatase and γ -glutamyl transferase (Choudhary et al. 2008). The change of enzymatic activity by MAL may be a direct consequence of MAL-induced damage of seminiferous epithelium (Uzun et al. 2009; Slimen et al. 2014). Moreover, Contreras and Bustos-Obregón suggested that MAL has a teratogenic effect on mice spermatid differentiation, perhaps due to an alkylating effect that disturbs the normal assembling of tail structural protein components (Contreras and Bustos-Obregón 1999). Furthermore, exposure to MAL was associated with reduced levels of FSH, LH, and testosterone (Uzun et al. 2009; Slimen et al. 2014).

The effect of MAL on the male reproductive system may be explained in terms of MAL capacity to induce an oxidative stress condition, by enhancing ROS production and lipid peroxidation, and reducing ferric reducing antioxidant power (FRAP) activity within testicular tissue (Bhardwaj et al. 2018). ROS may induce DNA damage and activates apoptotic pathways. It has been found that MAL disrupts the seminiferous epithelium proliferation, by impairing steroidogenesis, and that induces DNA fragmentation and apoptosis (Penna-Videau et al. 2012; Bhardwaj et al. 2018). MAL-induced increase in spermatogenic apoptosis rate was confirmed by

modified protein expression of p53, Bax, and Bcl-2, which facilitate apoptosis initiation (Penna-Videau et al. 2012; Bhardwaj et al. 2018). Although it has been documented that MAL exerts its cytotoxic outcomes, via direct effects on mitochondria by the induction of apoptosis, which may be due to increased ROS activating apoptotic pathways, the apoptotic effects may also be explained in terms of MAL-genotoxic effects that alter gene expression without mutation (Geng et al. 2015a, 2016). Another possible mechanism may be the induction of RNA and DNA alkylation, leading to mutagenesis, sperm morphology disruption, or teratozoospermia (associated with a high risk of apoptosis) (Agarwal and Said 2005; Penna-Videau et al. 2012). Thus, the decreased number of sperm cells and spermatozoon may be caused by increased apoptosis associated with MAL exposure (Geng et al. 2015a, 2015b).

The abnormal levels of reproductive hormones induced by MAL may also play important roles (Yu et al. 2011). MAL was found to probably affect the hypothalamic-pituitary-gonadal axis leading to a consequent reduction in pituitary gonadotrophins, follicular stimulating hormone (FSH) and luteinizing hormone (LH), and testosterone (Uzun et al. 2009; Slimen et al. 2014). Krause and Homola (1974) proposed that the decreased testosterone level might be due to direct damage of Leydig cell or to lowered stimulation of these cells by LH (Krause and Homola 1974). The probable effect of MAL on the male reproductive system needs further study and reconsideration of the daily allowed dose of MAL, especially in developed countries with extensive use of pesticides.

Female reproductive system OP-specific effect on the female reproductive system is not clear. It is believed that OPs, including MAL, disturb normal ovarian function resulting in a high incidence of atresia and apoptosis of granulosa cell that may consequently lead to loss and atresia of ovarian follicles (Bhardwaj and Saraf 2014). Koc et al. reported that MAL exposure reduced the ovarian size of adult Wistar rats, and the effect was dose-dependent (Koc et al. 2009). In 2016, Ozsoy et al. and Bhardwaj and Saraf studied biochemical, histological alterations induced by MAL on ovarian tissues. They concluded that acute MAL exposure significantly reduced ovarian antioxidant defenses, SOD, and catalase activity, as compared with the control group (Ozsoy et al. 2016; Bhardwaj and Saraf 2016). Increased MDA and reduced GSH were also observed, confirming the role of oxidative stress in MAL-induced toxicities (Koc et al. 2009; Arab et al. 2018). In addition, MAL exposure was associated with histopathological alterations in the ovarian tissue, such as hemorrhage, edema, decreased number of healthy follicles, increased number of atretic follicles, follicular degeneration, and infiltration of inflammatory cells (Koc et al. 2009; Ozsoy et al. 2016). Moreover, granulosa cells showed highly condensed or marginated chromatin with a fragmented nucleus, pyknosis, loss

of membrane integrity, increased empty spaces, and vacuolization in response to MAL treatment (Bhardwaj and Saraf 2016). Additionally, MAL exposure caused a significant decrease in mice oocyte survival and affected genes encoding proteins involved in transcription (BP75), translation (ribosomal protein S5), and mitochondrial function (cytochrome oxidase subunits I and III), in such a way that provides an evidence for MAL toxicity on mammal oocytes during the early oogenesis (Bonilla et al. 2008).

In addition to oxidative stress, the effect of MAL on the ovarian tissue may be induced by a change in hypothalamus-pituitary-gonadal axis. Uluitu et al. reported that chronic administration of MAL in female rats was associated with increased cerebral serotonin levels, during the active phases of the gonadal cycle (proestrus + oestrus), and this was accompanied with a decrease of LH synthesis and release and increase of the FSH release. Thus, MAL effect on the ovaries may involve affecting the reproductive encephalic regulatory serotonergic and acetylcholinergic, in addition to affecting pituitary gland hormones (Uluitu et al. 1981). Other studies suggested that oxidative stress is the key player that mediates MAL-induced ovarian toxicity by changing the physiology of ovarian follicles, inducing apoptosis and follicular atresia (Koc et al. 2009; Ozsoy et al. 2016). Bhardwaj and Saraf found a negative relationship between follicular apoptotic incidence and the activity of antioxidant enzymes, highlighting the role of oxidative stress in MAL-induced ovarian damage (Bhardwaj and Saraf 2016). Another possibility may be that MAL mediates apoptosis by distinct mechanisms such as inhibiting compensatory ovarian hypertrophy (Asmathbanu and Kaliwal 1997).

The effect on humans was supported by only one clinical study documenting that a high level of MAL, in the follicular fluid in women, was correlated with thinner endometrial thickness and lower retrieval and fertilization. Thus pesticide exposure may also adversely affect embryological intracytoplasmic sperm injection outcomes (Al-Hussaini et al. 2018).

Effect of malathion on the thyroid gland

MAL is not listed as a primary thyroid toxic chemical. However, recent evidence found that MAL affected thyroperoxidase catalyzed iodide oxidation, which affected thyroid hormone transportation and increased incidence of parathyroid hyperplasia (Mora et al. 2016; Xiong et al. 2018). The effect of MAL on the thyroid gland in humans was supported by a study reporting the association between hypothyroidism and MAL in male applicators (Goldner et al. 2013). Akhtar et al. reported decreased T3 and T4, which was accompanied by increased TSH in rats treated with MAL (Akhtar et al. 1996). Subsequently, Xiong et al. investigated the effects of MAL, on the thyroid gland, using Fischer rat

thyroid follicular cell line. They found that both mRNA and protein expression of thyroglobulin were significantly inhibited, and cAMP level and thyroid stimulating hormone (TSH) receptor expression were reduced by MAL (6.0 µg/ml). The results suggested that MAL disrupts the synthesis of thyroid hormone, probably by downregulating TSH receptor and cellular cAMP. This led to the inhibition of TSH-dependent signal transduction, thyroglobulin transcription, and thyroid hormone biosynthesis (Xiong et al. 2018). This explains reduced T3 and T4 level, with an increase of TSH as a feedback mechanism, observed by Ghisari et al. (2015). Another mechanism that may be involved in MAL-induced thyroid affection is by antagonizing aryl hydrocarbon receptors (Ghisari et al. 2015).

Mutagenic and carcinogenic potential

Pesticide exposure was correlated with genotoxicity and carcinogenicity in human and nonhuman subjects. Case control analyses of occupational exposures to OPs concluded positive correlations with non-Hodgkin lymphoma in the USA (Waddell et al. 2001), Canada (McDuffie et al. 2001), and Sweden (Eriksson et al. 2008). Occupational exposure was also correlated with increased risk of prostate cancer in Canada (Band et al. 2011). Furthermore, it was reported that in-utero environmental exposure to pesticides is associated with the development of childhood leukemia (Ferri et al. 2018; Hyland et al. 2018).

MAL is an already known mutagenic agent targeting DNA (Rupa et al. 1988; Lu et al. 2012). MAL was classified as “probably carcinogenic to humans” (Group 2A) by the International Agency for Research on Cancer (IARC) (Guyton et al. 2015). It was found to increase hepatocellular adenoma and carcinoma in mice and rats (Reuber 1985; Guyton et al. 2015). Moreover, one study found an evidence

of a positive correlation between MAL exposure and thyroid cancer (Brasil et al. 2018). MAL exposure was also associated with increased risk of lung cancer in rats and the risk increased by cofactors, such as estrogen (Echiburú-Chau and Calaf 2008). Epidemiological studies and meta-analysis found a positive association between exposure to MAL and increased risk of leukemia and lymphoma, and the risk increases when MAL is used in combination with other pesticides (Hohenadel et al. 2011; Navarrete-Meneses et al. 2017). On the other hand, a relatively recent AHS analysis of male applicators found null associations with MAL use and non-Hodgkin lymphoma (Alavanja and Bonner 2012; Hu et al. 2017).

In addition, several studies reported the role of MAL in breast cancer. One of these studies was conducted by Cabello et al., who found that MAL increased cell proliferation of terminal end buds of the mammary glands of 44-day old rats, followed by the formation of mammary adenocarcinomas, after about 28 months (Cabello et al. 2001). Similar results were observed by Omran and Omar, in which MAL induced breast atypical hyperplasia and malignant changes (Omran and Omer 2015). A correlation between MAL exposure and breast cancer in Hispanic agricultural workers in California was also documented (Mills and Yang 2005).

The carcinogenicity of MAL may be directly related to MAL-induced genotoxicity (Fig. 5). The genotoxicity of MAL had been previously studied, and it is suggested that MAL and its metabolite, malaoxon, can induce DNA breaks, micronuclei, chromosomal aberrations, and sister chromatid exchanges, with malaoxon being more damaging than MAL (Moore et al. 2011; Josse et al. 2014; Navarrete-Meneses et al. 2017; Abdel-Salam et al. 2018). Genotoxicity was observed in both animals and humans (Moore et al. 2010; Bianchi et al. 2015). They may induce DNA breakage at sites of oncogenes or tumor suppressor genes, thus explain the mutagenicity and carcinogenic potential (Salvadori et al. 1988; Błasiak et al.

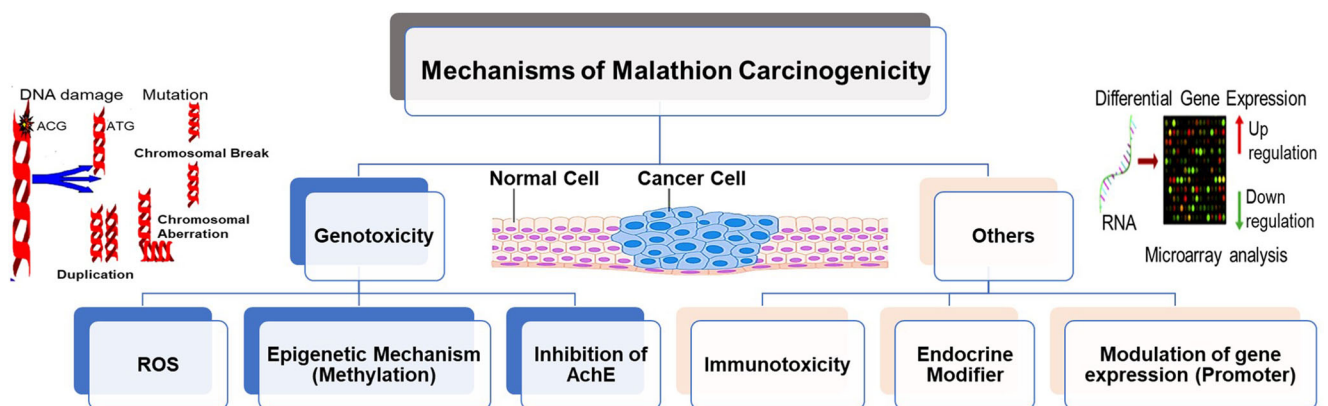


Fig. 5 Mechanisms of malathion-induced carcinogenicity. Malathion can induce carcinogenicity via its genotoxic effect. Malathion may induce genotoxicity through reactive oxygen species (ROS); ROS has the potential to induce DNA breaks and chromosomal aberrations. Other

neurotoxic mechanisms include DNA methylation and/or acetylcholine esterase (AChE) inhibition. Malathion carcinogenicity may be also mediated through modulation of gene expression, modification of endocrine hormones or receptors, and immunotoxicity

1999). It was found that MAL induces aberrations in KMT2A-AFF1 and ETV6-RUNX1 genes involved in the etiology of leukemia and lymphoma (Navarrete-Meneses et al. 2018). Furthermore, *in vitro* studies showed that MAL induced malignant transformation of breast epithelial cell lines, through genomic instability altering p53 (tumor suppressor gene) and oncogenes (Calaf and Roy 2008; Calaf et al. 2009).

Most probably, MAL-induced DNA breaks may be mediated through ROS, especially NO or its reactive metabolites, e.g., ONOO⁻, as the effect of MAL was minimized by 7-NI (a NOS inhibitor) (Blasiak and Stańkowska 2001; Abdel-Salam et al. 2017). Another possible genotoxic mechanism is through modifying gene promoter DNA methylation levels, thus acting via an epigenetic mechanism, and this may contribute to MAL carcinogenic potential (Zhang et al. 2012); malaoxon was found to methylate DNA bases (Blasiak and Stańkowska 2001). Others suggest that MAL induces genotoxicity and carcinogenicity through the inhibition of AChE as it was partially antagonized with atropine (Cabello et al. 2001; Calaf and Echiburú-Chau 2012) (Fig. 5). The genotoxicity of MAL was reported in Hepa RG (Josse et al. 2014), HepG (2) cells (Moore et al. 2010), blood lymphocytes (Ojha and Gupta 2015), and human choriocarcinoma cell line (Galántai et al. 2011), in addition to liver, brain, kidney, and spleen (Ojha et al. 2013).

MAL was also found to modify gene expression, which also plays a role in carcinogenicity, e.g., it was found to suppress proapoptotic Bax in breast tissues (Omran and Omer 2015). Recently, Anjitha et al. found that MAL upregulated or downregulated about 600 and 3500 genes in human lymphocytes, and about 57 of these genes are implicated in the etiology of cancer, such as genes involved in cell growth and differentiation, oncogenes, and signal transduction pathways like MAPK and RAS (Anjitha et al. 2020).

Other postulated mechanisms of MAL-associated carcinogenic potential may include immunotoxicity (Galloway and Handy 2003; Battaglia et al. 2010) and endocrine-disturbing effects. MAL exhibited weak estrogen receptor induction effect, caused changes in sex hormones circulation levels, and thus can promote the proliferation of hormone-related cancers (Kjeldsen et al. 2013; Lerro et al. 2015) (Fig. 5).

Immunomodulation

The immune system is very sensitive to a variety of environmental chemical and physical stressors, such as pesticides, which interfere with its function. The outcome of immune dysfunction may appear as a reduction in the resistance to infectious diseases and cancer or induction, facilitation, or exacerbation of allergy and autoimmune disorders (Jorsaraei et al. 2014). Increased incidence of immune-related disorders due to exposure to chemicals has been observed, including OPs and MAL (Corsini

et al. 2013). Mechanisms include genotoxicity that may end with mutations in the genes coding for immunoregulatory factors, modification of immune tolerance, and activation of implicated pathways, such as inflammatory and apoptotic pathways (Corsini et al. 2013).

Experimental studies proved that OP compounds can directly increase the secretion of pro-inflammatory cytokines. The increase in pro-inflammatory cytokines such as NF-κB, TNF-α, INFγ, IL-6, IL-4, IL-1β, and IL-10 was observed in rats treated with MAL (Ince et al. 2017; Mohammadzadeh et al. 2018). Dhoub et al. found that MAL also enhanced the expression of IFN-δ in the liver of MAL-treated rats, which causes increased proliferation of immune cells such as leukocytes, neutrophils, and lymphocytes, as a direct consequence. Cytokine levels returned to control values 1–2 days after exposure, but a second increase in cytokine levels was observed in some rats 1 month later, indicating that inflammation can persist long after the initial exposure. MAL-induced leucocytosis may also be caused by the release of catecholamine as a stress hormone, which causes demargination of neutrophils, and is accompanied by lymphocytosis and by monocytosis (El-Bini Dhoub et al. 2015). In addition, MAL increased the number of total CD4+ and CD8+ T cells in the spleens of exposed rats. The increase in T cell indicates an activation of the immune system in response to a xenobiotic and proves that MAL induces inflammation. It is possible that MAL may act directly on T lymphocytes, inducing activation of cell proliferation (El-Bini Dhoub et al. 2015).

Moreover, Johnson et al. reported an increased antibody production following immunization with a T lymphocyte-dependent antigen in female mice treated with MAL at doses as low as 0.018 mg/kg, which is below the human allowable daily intake (0.02 mg/kg) (Johnson et al. 2002); their results were in agreement with those of Flipo et al. (Flipo et al. 1992). This may explain the report of Sozeri et al. of 2 children with generalized cutaneous sclerosis, with signs correlated to exposure to pesticides containing MAL (Sozeri et al. 2012). Another study revealed that weekly administration (> 33 mg/kg) elevated the level of serum rheumatoid factor at 19 weeks of age, and a higher dose (> 100 mg/kg) also increased the level of anti-DNA antibodies in the serum of MRL-lpr mice (mice genetically predisposed to autoimmune disease) (Rodgers 1997). Malathion thus may be a possible player in development of an autoimmune disease, especially in predisposed individuals. However, further data still need to be collected.

On the other hand, many studies in rats showed that MAL induced immunosuppression (Zabrodskii et al. 2015; Ramadan et al. 2017). Mechanisms include the decrease of the count of blood leukocytes, granulocytes or agranulocytes,

weights and cellularity of lymphoid organs, and humoral and cellular immune responses (as indicated by the decrease in the serum γ -globulin concentration and the delayed-type of hypersensitivity response, respectively) (Zabrodski et al. 2015; Ramadan et al. 2017). In addition, it was found that MAL induced shrinkage and distortion of lymphatic follicles of the spleen and degeneration of most bone marrow cells (Ramadan et al. 2017). Moreover, Zabrodski et al. reported that subacute exposure of rats to MAL suppressed both humoral and cellular immune responses and reduced the function of Type 1 helper cells (Th1) and to a lesser extent Th2 lymphocyte, as well as significantly decreased the level of blood cytokines: TNF α , IL-1 β and IL-6, IFN- γ , IL-2, and IL-4 (Zabrodski et al. 2015). Additionally, MAL was found to induce lymphocytes' DNA adduct formation, which leads to apoptosis that is partially mediated by activation of intracellular caspases (Ojha and Gupta 2017). Seth et al. (2001) found changes in GSH and γ -glutamyl transpeptidase level in lymphocytes in humans intoxicated with MAL (Seth et al. 2001).

Thus, the effect of MAL on the immune system is well documented in experimental animals; the alteration between either immunosuppression or immunostimulation may be a factor of the dose and duration of exposure, experimental design, nutritional status, and innate immunity. However, the available studies on the effects of MAL on human's immune system is not sufficient, and further studies are necessary (Corsini et al. 2013).

Other malathion-related toxic effects

Effect on blood cells

MAL was shown to induce normocytic normochromic anemia, thrombocytopenia, and prolongation of the clotting time (Ramadan et al. 2017). Hematotoxic activity may be attributed to the decrease in hematopoiesis due to bone marrow suppression, an increase in the rate of erythrocytes breakdown, internal hemorrhage, and a reduction in clotting factors production resulting from liver toxicity (Durak et al. 2009; Kundu and Roychoudhury 2009). Under normal conditions, erythrocytes are resistant to hemolysis resulting from peroxidative reactions, by the help of antioxidant enzymes and molecules; SOD, GPx, catalase, and GSH. Excessive ROS production, associated with MAL-induced oxidative stress and reduction in antioxidant defenses, may be associated with increased hemolytic oxidative injury of erythrocytes (Fakhri-Bafghi et al. 2016; Farag and Alagawany 2018). MAL was found to increase lipid peroxidation and deplete antioxidant defenses in rats and human erythrocytes (Uzun et al. 2009; Ramadan et al. 2017). Akhgari et al. found that oxidative stress and the degree of erythrocyte lipid peroxidation was correlated with the degree of inhibition of erythrocytes AChE (Akhgari et al. 2003; Farag and Alagawany 2018).

Acute pancreatitis

Previous reports have suggested that acute pancreatitis may follow the oral ingestion of several OPs (Hsiao et al. 1996). MAL may also induce pancreatic- β -cells injury, hyperglycemia, temporary hyperinsulinemia, and oxidative stress (Tuzcu et al. 2014). A case report of a combination of acute pancreatitis and toxic hepatitis, which developed in a 30-year-old farmworker, was provided by Findikli et al. (2018). The possible pathogenesis of the pancreatic injury may be excessive cholinergic stimulation of the pancreas and ductular hypertension (Hsiao et al. 1996).

Lung injury

Many OPs are implicated in the development of pulmonary injury in both humans and experimental animals (Atiş et al. 2002; Nambiar et al. 2007; Moin-Azad Tehrani et al. 2011; Angelini et al. 2013). It is possible that these chemicals are directly affecting the viability of the pulmonary epithelium resulting in pulmonary distress (Angelini et al. 2015). Uysal and Karaman (2018) revealed that acute oral MAL administration increased oxidative stress and apoptosis in the lung tissue of rats. Tissue GPx and SOD activities decreased and MDA level and the expression of proapoptotic proteins Bax and caspase-3 significantly increased in the MAL-treated group (Uysal and Karaman 2018). Furthermore, thickened lung epithelium was also observed (Saadi et al. 2008). In another study, malaoxone (the toxic metabolite of MAL) induced apoptotic cytotoxicity of primary cultured human large and small airway cells, associated with the upregulation of caspases (Angelini et al. 2015). Thus, there is evidence of pulmonary risk associated with MAL not only in animals but also in human.

Pre- and post-natal exposure toxicity

In recent years, a growing body of evidence indicates the high vulnerability of pregnant/lactating women concerning pesticide exposures (Berkowitz et al. 2003; Salas et al. 2003). Many studies report neurotoxicity to be linked to perinatal exposure to OPs in animals (Slotkin et al. 2005; da Silva et al. 2006). Both high and low levels of OP exposure may have a serious impact on pregnant women and children (Sapbamrer and Hongsibsong 2019). Children are more vulnerable than adults because of the incomplete nature of the detoxification process, the age-related speed of neurologic development, the increased exposure relative to the body weight, and the undeveloped immune system (Eskenazi et al. 1999; Fiedler et al. 2015). The major concerns related to prenatal and postnatal exposure in children is neurodevelopmental impact. Exposure to pesticides in a period of great vulnerability is a major factor in causing

dysfunction in the nervous system and neurodevelopmental disorders (Landrigan et al. 1999; Heyer and Meredith 2017).

Bossi et al. found that both MAL and its metabolite appear in the amniotic fluid of female rats, and thus the fetus is exposed to them (Bossi et al. 2013). Several studies reported the effect of prenatal and postnatal exposure to MAL. Prabhakaran et al. found that MAL exposure during pregnancy induces maternal toxicity in mice and causes fetal growth retardation. MAL effects were aggravated with protein-deficient diet, GSH depletion, and decreased activities of GPx, glutathione reductase, and glucose-6-phosphate dehydrogenase (Prabhakaran et al. 1993).

Da Silva et al. studied the effect of MAL exposure through lactation in mice. They found that MAL exposure induced significantly high inhibitory effect on AChE in the brain of the offspring even at the lowest dose (20 mg/kg); however, AChE activity in the mother was inhibited only at the higher dose (200 mg/kg) (da Silva et al. 2006). This may be explained by reduced metabolizing detoxifying capacity in neonates. Similarly, Selmi et al. reported that MAL exposure during lactation induced a high inhibitory effect on the brain, plasma, and erythrocyte AChE activities in rat pups and was also associated with increased oxidative stress (Selmi et al. 2012). MAL was also detected in human milk in women from Bhopal, India, who used MAL as a pesticide. The offspring were found to receive 4 times more MAL than the average daily intake recommended by the World Health Organization (Sanghi et al. 2003). Gunier et al. found an adverse relationship between the agricultural use of neurotoxic pesticides near maternal residences during pregnancy and the IQ of 7-year-old children (Gunier et al. 2017).

The effect of MAL on the reproductive function and neurodevelopment in young rats is more pronounced when combined with other pesticides (synergism) (Moser et al. 2006; Yu et al. 2013).

Since ACh plays important trophic roles in brain development, thus excessive exposure during the developmental period can lead to abnormal neurodevelopment by modifying the timing or the intensity of ACh neurotrophic actions (Slotkin 2004). Moreover, MAL has direct effects on cellular processes, such as oxidative stress, which can affect brain development and are unrelated to the inhibition of AChE (Slotkin 2004; Selmi et al. 2012). Hepatotoxicity and nephrotoxicity were also observed by Selmi et al. in rat pups exposed to MAL through breastfeeding (Selmi et al. 2015).

Therefore, the state of knowledge of pregnant women and nursing mothers should be updated to help them protect themselves and their children from exposure to pesticides.

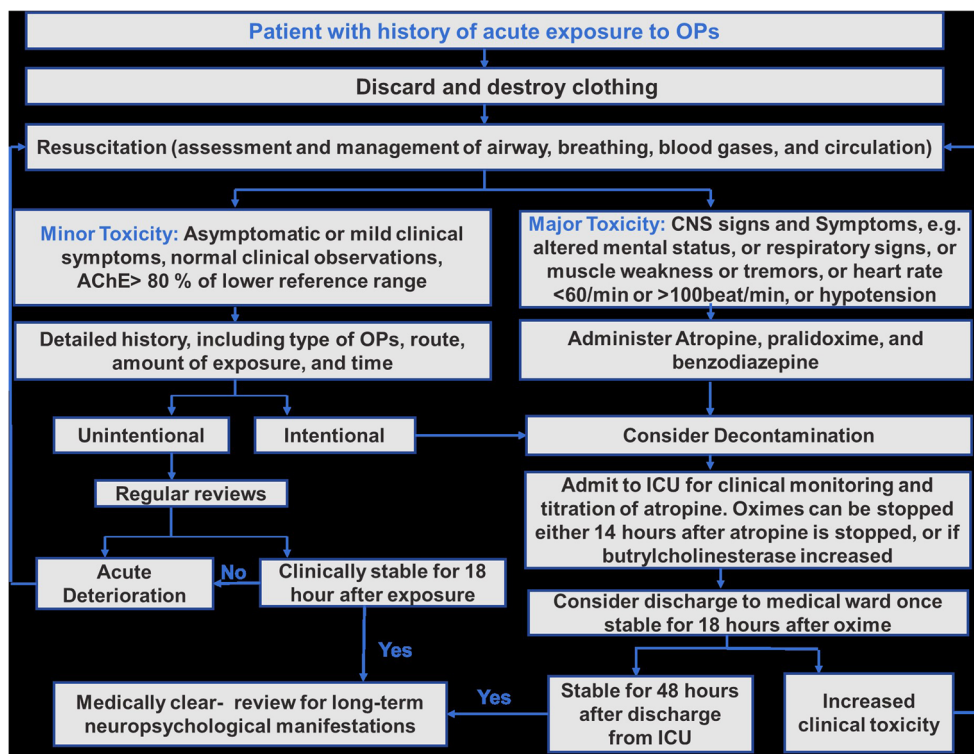
Protection and management of MAL toxic exposures

Treatment of MAL toxicity

Classical measures

Acute MAL toxicity can be treated as ordinary OP toxicity; however, acute toxicity incidence is relatively low. The primary cause of death after an AChE inhibitor poisoning is respiratory

Fig. 6 Planned recommendation for the management of patients presenting with a history of acute organophosphorus poisoning. Figure modified from that of Roberts and Aaron (2007). AChE acetyl cholinesterase, CNS central nervous system, ICU intensive care unit, OPs organophosphates



failure and hypoxemia due to muscarinic effects on the cardiovascular and pulmonary systems (i.e., bronchospasm, aspiration, bradycardia, or hypotension), nicotinic effects on skeletal muscles (weakness and paralysis), loss of central respiratory drive, and seizures (rare). Initial treatment for acute MAL toxicity is mainly concerned with ensuring an adequate airway, oxygenation, and ventilation and stabilizing patient hemodynamics by reversing excessive muscarinic effects, mainly by using atropine (Eddleston et al. 2008; Eddleston 2019). Once the patient is stable, the administration of an AChE-reactivating drug, such as pralidoxime or obidoxime, should be considered along with skin and/or gastric decontamination (Roberts and Aaron 2007) (Fig. 6). Benzodiazepines are to be used for patients with agitation and seizures.

Novel treatments for MAL poisoning

Lipid emulsions Intralipid is the brand name of the first safe fat emulsion developed for human use and was introduced in 1962. Intravenous lipid emulsion (ILE) is always used in parenteral nutrition therapy. ILE has proved to be an effective treatment for local anesthetic systemic toxicity in humans and animals and is promising as a novel antidote for a wide range of other lipophilic drug poisonings (Ozsoy et al. 2016). ILE seriously improved TAC in rats with MAL-induced neurotoxicity (Basarslan et al. 2014), restored SOD activity considerably in the ovarian tissue, partially improved histopathological changes, and inhibited MAL-induced upregulation of caspase-3 (Ozsoy et al. 2016). Uysal and Karaman (2018) study suggests that ILE has treatment efficacy on MAL-induced lung toxicity (Uysal and Karaman 2018). Evidence of protective effects on pancreatic (minimized pancreatic- β -cells) and hepatic damage caused by MAL, using intralipid fat emulsion, was also found (Tuzcu et al. 2014; Esen and Uysal 2018). That ILE is a promising safe therapy for acute MAL intoxication. Beside lipid sink theory, the use of fatty acids contained within the ILE as a good source of energy might have provided a protective mechanism against apoptosis by further increasing the ATP levels in the cells (Esen and Uysal 2018).

Magnesium and calcium channel blockers The use of magnesium or calcium channel blockers such as nifedipine in OP poisoning has long been advocated (Petroianu et al. 1998; Brvar et al. 2018). Both preclinical and clinical data suggest that they might be promising adjunct treatments. However, the evidence is currently insufficient to recommend their use, and the precise mechanism of how they might work remains unclear (Brvar et al. 2018; Eddleston 2019). Mohammadi et al. found that magnetic isotopes of magnesium significantly recovered MAL-induced arrhythmia and cardiac failure in rats (Mohammadi et al. 2011). Recently, Hsu et al. revealed that MAL toxicity in glial cells was associated with the stimulation of Ca^{2+} -signal transduction and induction of Ca^{2+} -associated

cytotoxicity (Hsu et al. 2019). This may explain the role of calcium channel blockers in OP toxicities.

Potential protective measures against long-term effects of MAL exposure

Several studies document the protective effect of different antioxidants and minerals against toxic effects associated with MAL exposure. Treatment with antioxidants or mineral substances can decrease lipid peroxidation and oxidative stress related to MAL-induced toxicity (Ince et al. 2017; Akbel et al. 2018). Among those are N-acetyl cysteine (Bhardwaj et al. 2018), vitamin E and C, selenium (Durak et al. 2009; Uzun et al. 2009; Aboul-Soud et al. 2011; Lu et al. 2012), α -lipoic acid (Omran and Omer 2015), and taurine amino acid (Ince et al. 2017), which have shown promising protective effects against different organs' toxicity that was induced by MAL.

Natural compounds are gaining much attention, as being considered safer and can be used daily on highly exposed persons. Many natural compounds showed potential protective activity against various types of toxicities (Madrigal-Santillán et al. 2014; Wu et al. 2017). Polyphenols, such as flavonoids, anthocyanins, and phenolic acids, are powerful antioxidant substances (Madrigal-Santillán et al. 2014), and many of them approved efficacy against MAL-induced tissue damage. Akbel et al. found that resveratrol reduced the level of malaoxon in different tissues and counteracted the toxic effects of MAL and maintained antioxidant defenses (Akbel et al. 2018). Ginger and zinc mixture ameliorated the toxic effect of MAL in the liver and the kidney due to its antioxidant effect (Baiomy et al. 2015). Mohammadzadeh and his colleagues found that crocin, saffron active components, exhibited protective effects against MAL-induced Parkinson-like behavior through reducing lipid peroxidation, improving motor deficits and anti-inflammatory effects (Mohammadzadeh et al. 2018). Other natural products that approved efficacy include aged garlic extract (Ramadan et al. 2017), grape seed extract (Abdel-Salam et al. 2018), *Aloe vera* (Gupta et al. 2019), caffeic acid (Rezg et al. 2015), thymoquinone (Abdel-Daim et al. 2020), and curcumin (Alp et al. 2012). Recommendations for increasing the use of these antioxidants on a daily basis, especially those working in pesticides' factories or agriculture, may be warranted.

Few data support the possible effectiveness of anti-inflammatory drugs in ameliorating MAL toxicity; one study used acetylsalicylic acid and dexamethasone to ameliorate MAL-induced neurotoxicity. The use of anti-inflammatory drugs was associated with improved neurobehavioral performance and reduced neurodegeneration in the nigrostriatal system (Ahmed et al. 2017). Another study showed that the use of dexamethasone improved a case of nephrotic syndrome that was associated with MAL (Yokota et al. 2017). Further studies

regarding the effectiveness of anti-inflammatory drugs against MAL-induced toxicity are needed.

One new trend in therapy, which is still not investigated in OP toxicity, is probiotics. Trinder et al. reported that lactobacilli are able to degrade some pesticides and reduce the accumulation of mercury and arsenic. So, they assume that similar effects may take place with OPs including MAL, given that the lactobacilli can also attenuate ROS production, enhance gastrointestinal barrier function, reduce inflammation, and modulate host xenobiotic metabolism (Trinder et al. 2015). Probiotics, if proven effective, will represent a convenient and cost-effective protective measure against MAL toxicity, especially neurotoxicity (as the gut-brain axis is being extensively studied nowadays). I thus recommend the use of probiotics in MAL-induced toxic experimental models to assess their potential protective value.

Conclusion

MAL toxicity is well documented, affecting nearly every tissue in the body. Special consideration to prenatal and postnatal exposure and those exposed during occupation may be needed. MAL toxicity was reported to occur experimentally at doses lower than the daily allowed ones, so reconsideration of the allowed level may be necessary. Nutritional status and the combined use of pesticides play a significant role in amelioration or potentiation of toxic effects. Further studies are needed regarding the carcinogenic and genotoxic effects in humans and potential protective measures.

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Compliance with ethical standards

Conflict of interest The author declares that she has no conflict of interest.

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