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Review Paper

The insect repellents: A silent environmental chemical toxicant to the health

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ABSTRACT

In recent years, a large number of insect repellents have been developed with the idea of consumer benefits. In addition to already known advantageous application of insect repellents, there is increasing concern about the potential toxicity in environment leading to health caused by random use of these compounds. An increasing number of evidence suggests that insect repellents may trigger undesirable hazardous interactions with biological systems with a potential to generate harmful effects including intermediate metabolites. Biotransformation followed by bioaccumulation (*vice e versa*) may be an important phenomenon for toxic response of this chemicals. In this review, we have summarized the current state of knowledge on the insect repellent toxicity, including biochemical pathway alteration under *in vitro* and *in vivo* conditions considering different classes of organisms, from lower to higher vertebrate. Furthermore, we have tried to incorporate the effects of insect repellent in light of some clinical reports. We hope this review would provide useful information on potential side effects of uncontrolled use of insect repellents.

Contents

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1. Introduction

The ecosystem is continuously exposed to ever-increasing pressure due to the presence of emergening contaminants, especially personal care products including deodorant, eye liner, lipstick, lotion, perfume, shaving cream, moisturizer, talcum powder, toothpaste, cleansing pads, cotton swabs, wet wipes etc. (Quantin et al., 2015). Current knowledge about the contaminants of these products has significant gaps regarding their toxicity towards human beings. Moreover, bioaccumulation and metabolites formation through biotransformation of these products have raised serious concerns related to endocrine disruption, allergic contact dermatitis, asthma attacks and migraine (Yazar et al., 2011; Celeiro et al., 2014). Specifically, insect repellents that are being used by the people from ancient age contain harmful chemical groups, causing concern to the human health.

In this review, we aim to report the overall toxic effects of insect repllent exposure to different animal model including clinical outcome time to time based on available literature in medical database (Fig. 1). Several plants having insect repelling properties are native to tropics where they are grown for a wide range of medicinal purposes. In different countries, these native plants have a history of use for personal protection against insects. Numerous studies reveal that essential oils extracted from plants demonstrate promising insect repellent activity (Trongtokit et al., 2005). These active ingredients are used for further development to new formulations of insect repellents that might have shown better alternative affects against insects.

The toxicity of insect repellent is largely dependent upon the route of exposure along with level of doses. There are four ways that people gets exposed to chemicals present in the specific insect repellent: skin contact, eye contact, breathing in, and unknowing ingestion (Dimitroulopoulou et al., 2015). The most common unintentional route of exposure is ocular and nasal route due to formulations, most of which are ususally sprays in liquids/gaseous form. Picaridin, a widely used repellent is often applied directly on skin. It may also be inhaled when sprays are used around the body, especially in indoor spaces where the vapors being retained for some duration. If the users don't wash hands after applying an insect repellent and then smoke or handle food, it is quite possible that they may swallow some picaridin (Charlton et al., 2016). Other insect repellents like *N*,*N*-diethyl-3-methylbenzamide (DEET) causes local irritation and discomfort when introduced into the eyes or oral cavity. Ingestions of DEET have also been associated with nausea, vomiting, hypotension, encephalopathy, seizure, coma, and ataxia (Chen-Hussey et al., 2014). Excessive dermal application of DEET to large areas of the body over a period of days to weeks, especially in children, has led to seizures, bradycardia, nausea, vomiting, bullous eruptions, lethargy, ataxia, encephalopathy and anaphylaxis (Clem et al., 1993; Miller, 1982; Briassoulis et al., 2001). Some form of neurotoxicity is most commonly reported as systemic toxic effect of insect repellents but some of their mechanisms of action are still unknown. The important physicochemistry properties of insect repellents, which are widely studied have been highlighted (Table 1). These properties are important to make repellent sprays in liquids/gaseous form.

2. Toxicity study of insect repellents

2.1. N, N-*diethyl-3-methylbenzamide*

N, N-diethyl-3-methylbenzamide (DEET) is a synthetic insect repellent that is found at various concentrations in surface waters of environment. DEET was first developed for military use in US Army in 1944 (Katz et al., 2008). Information regarding DEET's toxicity in the environment as well as organisms is still limited and is focused only on its acute effects on specific model. DEET is the active ingredient of many commercial insect repellents (Antwi et al., 2008). Despite being detected worldwide in effluents, surface water and groundwater, there is still limited information on DEET's toxicity toward non-target aquatic invertebrates. DEET seems to be most effective and is the best studied insect repellent currently available to the general consumer. Lactic acid is an important and probably an essential trigger to the insect for landing on the host. Therefore, the unique effectiveness of DEET is considered due to its ability to mask the sensory perception of lactic acid on the skin. In this way, DEET is primarily used to repel biting pests such as mosquitoes and ticks. DEET is also used in combination with insecticide to increase the potency (Moss, 1996). DEET is a chemical cmpound where *N*,*N*-diethyl-meta-toluamide, ortho and para isomers are present at low concentrations. DEET is an *N*,*N*-disubstituted aromatic carbonamide, which is used as an active ingredient in insect repellents. Technical grade DEET is typically formulated with carriers and solvents (such as ethanol, isopropanol, or water) for use in commercial products. Commercial product formulations include aerosol and non-aerosol sprays, lotions, creams, sticks, foams, and wipes. DEET concentration in commercial products varies according to countries and can range from 4 to 100% (by weight). Technical-grade DEET typically contains 95% meta-isomer, the most effective form of the chemical.

2.1.1. *Research findings*

2.1.1.1. *In vivo*

A recent study has reported the consequence of DEET exposure to a caddisfly, *Sericostoma vittatum* using sub-lethal doses (Campos et al., 2016a). Acute tests revealed an exposure of DEET caused feeding inhibition, along with a significant reduction of carbohydrates levels in *S. vittatum*. These results have added some important information for the risk assessment of insect repellents in the aquatic environment. Another group examined the effects of DEET in the life cycle of *Chironomus riparius* and evaluated its biochemical effects (Campos et al., 2016b). Importantly, DEET reduced developmental rates (reduced larval growth, delayed emergence) of *C. riparius* larvae and also caused a decrease in size of adult midges. Considering the biochemical responses, a short exposure of DEET significantly inhibited catalase, acetylcholinesterase and glutathione-S-transferase activities and reduced total glutathione contents, leading to neurotoxicity. Interestingly, the toxicological effect of DEET was also studied in mixotrophic dinoflagellates *Gymnodinium instriatum* (unicellular green alga) (Martinez et al., 2016). In this study, the effective concentration of DEET reduced oxygen flux by 50% for this species, which is more than five times lower than the EC50 reported previously for the unicel-