The Pharma Innovation Journal 2023; 12(5): 2730-2735

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2023; 12(5): 2730-2735

www.thepharmajournal.com
Received: 01-03-2023
Accepted: 06-04-2023

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A review on toxicity induced by the insecticide indoxacarb

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Abstract
The fight against agricultural and household pests accompanies the history of humanity, and chemicals have long been used to control pests. Despite environmental and health concerns, a total ban on the use of pesticides seems unlikely in the predictable future. Currently, less than 1% of the total amount of pesticides applied for weed and pest control reach the target pests therefore, chances of environmental exposure and exposure to non-target species is a legitimate concern. Efforts are being done to synthesize highly selective pesticides with less environmental side effects. Indoxacarb (IDX), is one of such pesticides and was introduced as a highly selective insecticide effecting sodium channel of insects. It is a member of new oxadiazine class of insecticide with an excellent activity against lepidopteran pests as well as those insects that have developed resistance to organophosphate (OP) and carbamate insecticides. In this review, various studies on the toxicity of IDX are discussed in order to enhance the understanding of indoxacarb toxicity, as accidental ingestion by livestock and subsequent chronic exposure may pose a threat to the health of animals.

Keywords: Indoxacarb, insecticide, toxicity, *in vitro*, *in vivo*

1. Introduction
The increase in population has resulted in a greater need for food production and this challenge is met by the use of pesticides that improve crop yields by providing protection from pests. These chemical agents have assumed a crucial role in changing the current global situation in food production as they are mainly used in agriculture and forestry. However, the issue of residues and bio-magnification of these chemicals pose a threat to human and animal health making them a matter of public health concern. At the same time, the risk of toxicity can be reduced if the users are skilled and aware of the pesticide being used, which unfortunately is not the scenario due to lack of awareness or negligence. Therefore, the disproportionate use of these chemicals adversely affects the health of flora and fauna, the soil ecosystem, as well as the aquatic system (Rajmohan *et al*., 2020) [26]. There are established "safe limits" for each of these pesticides and within this range they are generally considered safe. However, the safe level may underestimate the harmful impacts upon repeated exposure or simultaneous exposure to different pesticides. Dermatological, gastrointestinal, neurological, carcinogenic, pulmonary, reproductive and endocrine impacts are only some of the health consequences due to such exposures. Furthermore, unintentional exposure or wilful poisoning might be fatal (Nicolopoulou *et al*., 2016) [23].
Insecticides are the main class of pesticides used in agriculture and are also used as ectoparasiticides in veterinary medicine. The vast insect population is an obstacle to good and sufficient quantity of agricultural production and controlling insect population is also a necessity for the health of livestock and pet animals. Having said that, they are also one of the most misused group of chemicals. The health impact on the use and misuse of insecticides are enormous. Therefore, there is a need to produce a safe and selective insecticides and also is the need for comprehensive toxicity studies.
The recently introduced pesticide Indoxacarb (IDX) under oxadiazine class of insecticide is said to have an excellent activity. Reportedly, it also has comparably lesser health and environmental side effects (EPA, 2000) [7]. It is reported to be moderate to highly toxic to aquatic life and less toxic to mammals (Ghelichpoura *et al*., 2019) [11]. Since its introduction, the use of this compound has been increasing, but there is little data on the carcinogenicity of the compound. Therefore, it is necessary to assess the toxic potential - in terms of cytotoxicity and genotoxicity, due to the importance of the compound, the usage, the number of animals,

and people exposed due to their occupation, citizens dwelling in and around the agricultural land and the people consuming the residues.

2. Indoxacarb

The United States Environmental Protection Agency initially approved IDX in water dispersible granules and emulsifiable concentrate formulations in 2000, primarily for foliar treatment against lepidopteran pests of cotton, rice, apples, pears, sweet corn, lettuce and fruit. Recent studies have shown that IDX is quite potent in controlling cockroaches, ants, termites, flies and is commercialized as gel bait (Sandeep *et al*., 2016) [28]. It was developed by Du Pont Ltd., New Zealand as the first member of Oxadiazine class of insecticides against insects of crops, turf grasses and insect ornamentals. Various preparations of IDX include a spot-on for control of ectoparasiticides; a foliar spray in field, fruit and vegetable crops. It is larvicidal and is also effective against adults and eggs of many pests (National Registration Authority, 2000) [24].

The European Union approved IDX as a topical spot-on flea and tick control for dogs and cats and in combination with permethrin as a topical spot-on against flea and ticks for application in dogs only. It is a pyrazoline-type insecticide originally developed to act against insect strains that are resistant to the existing insecticides. It is neurotoxic and acts by inhibiting sodium channels. The sodium channel of insects is sensitive to nanomolar concentrations while the mammalian sodium channel is sensitive to micromolar concentrations of the drug and this form the basis of its selective toxicity towards insect pests (Gwaltney, 2013) [13]. However, the usage of neurotoxic chemical pesticides has resulted in environmental damage, insect resistance, and non-target organism adverse effects (Caballero *et al*., 2019) [6].

3. Mechanism of action and toxicokinetics

Absorption of IDX by insects is mostly via oral route or lesser through cuticle. It is bioactivated by cleaving of carbomethoxy group from the parent compound forming an active metabolite (Decarbomethoxyllated JW062) DCJW (Figure 2). This metabolite binds to and acts on the voltage gated sodium channel and inhibits the initiation of action potential within the insect's nervous system, resulting in paralysis and death (Lapied *et al*., 2001) [18]. IDX and its metabolite DCJW suppressed tetrodotoxin-resistant (TTX-R) voltage-gated sodium channels in the dorsal ganglion of rat neurons using whole-cell patch clamp technique (Tsurubuchi and Kono, 2003) [34]. While the ratio of active (S)- and inactive (R)- enantiomers in DPX-JW062 are 50:50, the active and inactive enantiomers in DPX-MP062 are 75:25 (Narahashi, 2001) [21]. IDX undergoes biotransformation in the German cockroach to a toxic metabolite DCJW which were further metabolised to hydroxy, oxadiazine ring-opened and hydroxylated ring-opened metabolites, which were NADPH/cytochrome P450-dependent (Gondhalekar *et al*., 2016) [12]. IDX also produces a dynamic modulating action on nicotinic Acetylcholine receptors (nAchRs). Additionally, it has also been implicated in the generation of severe oxidative stress, interference in inflammation and tissue damage (Ghelichpoura *et al*., 2019) [11].

IDX is about 60% absorbed by oral route. It is hazardous when taken orally, damaging when inhaled, and less toxic when applied topically. It is distributed in the body mainly in fat and red blood cells. It is found at a higher level in tissues of females. There is also species difference in which rats are more sensitive than mice and dogs. In the liver, the pesticide undergoes extensive metabolism. In rats, there is no build-up and it is eliminated in equal amounts in urine and faeces, whereas more amount of excretion occurs via faeces compared to urine in mammals. Only trace levels of the parent component were found in the faeces, and no amount was found in the urine (Arena *et al*., 2018) [4]. The structure–activity analysis of IDX revealed that the presence of a strong electron-withdrawing group and reduced steric hindrance of the indenone ring (R1, R2) in positions 5 and 6 might boost larvicidal activity and BgNav1-1a channel inhibitory activity (Hao *et al*., 2015) [14]. IDX induced hydrolytic activation by antagonizing the effect of S,S,S-tributylphosphorotrithioate (DEF), which is an inhibitor of hydrolytic metabolism (Alves *et al*., 2008) [3].

4. Toxicological studies of indoxacarb

4.1 *In vitro* studies

IDX is a highly efficacious and selective insecticide for use against insect insecticides with organophosphate, carbamate, and pyrethroid resistance. Sbartai *et al*. (2012) [29] used Paramecium, eukaryote unicellular, as an alternative model for testing of IDX. The evaluation of respiratory activity revealed a decrease in oxygen consumption, indicating that IDX had a negative effect. In a study conducted by Wing *et al*. (1998) [35], *Manduca sexta* larval instar was used to see the potency of the parent compound JW062 and the metabolite DCJW as a blocker of sodium channel in *M. sexta* larval motor nerve preparation *in vitro*. JW062 causes flaccid paralysis 4 hours post-injection while DCJW metabolite at the same dose produced neurotoxic symptoms within 10 minutes. The experiment proved that the DCJW was more potent in blocking the compound action potential (CAP) rather than the racemic JW062.

Caballero *et al*. (2019) [6] demonstrated the synergistic action of IDX and a pyrethroid insecticide, deltamethrin *in vitro* using cockroach neuro-secretory cells. The result showed that relatively low concentration of nano-encapsulated deltamethrin is efficient to optimize the effect of IDX on sodium channels while reducing the concentration of IDX.

FAO (2016) [9] reported that IDX does not induce reverse mutations in an *in vitro* bacterial assay with the bacteria *Salmonella typhimurium*. IDX was found to be non-genotoxic in *Salmonella typhimurium* and *Escherichia coli* reverse mutation assays at concentrations up to 5000 g/plate (with and without metabolic activation, as well as unscheduled DNA synthesis in hepatocytes of rats (up to 200 g/mL). Also, an *in vitro* test done on a mouse bone marrow micronucleus assay (1000-4000 mg/kg) reveals negative result (NRA, 2000) [24]. An experiment was performed by Shi *et al*. (2021) [31] on the potential involvement of NADPH-cytochrome P450 reductase (CPR) in the resistance of indoxacarb by *Spodoptera litura*. MTT cytotoxicity assay results indicated that the *S. litura* SlCPR-X1-expressed cells exhibited a significantly higher viability than the SlCPR-X2. So, IDX causes cytotoxicity by reducing cell viability.

4.2 *In vivo* studies

4.2.1 Immunotoxicity

Sandeep *et al*. (2016) [28] reported that IDX exposure induced immune-response changes in mice. Its combined exposure to

LPS and endotoxin caused significant damage such as lymphocytopenia. IDX did not cause DNA damage in the comet assay, but when combined with LPS, it caused the mice's tail length, tail moment, and olive moment to increase significantly. Exposure of zebrafish (*Dani orerio*) embryos to varying concentrations of (-)-R-IDX and (+)-S-IDX chiral isomers until 96-hours post-fertilisation was done to assess the embryonic toxicity. The rate of partial edema induced by (-)-R-IDX was 2.5 times that of (+)-S-IDX, and the heart rate was 30% lower in the former than the latter. A significant increase in apoptosis was also observed; interestingly, (-)-R-IDX induced apoptosis in the heart area, whereas (+)-S IDX induced apoptosis in the head area (Fan *et al*., 2017) [8].

Ghelichpoura *et al*. (2019) [11] investigated the effects of chronic IDX exposure on immunological, antioxidant, and stress gene expression in common carp, *Cyprinus carpio*. IDX exposure at low concentrations increased inflammatory cytokine gene expression (IL-1, IL-8, IL-10, TNF-, and IFN-), but exposure at higher concentrations decreased inflammatory cytokine expression. The expression of antioxidant genes (SOD and CAT) was measured in several tissues. Low amounts of IDX increased them to combat a primary oxidative condition, according to the findings. Higher IDX doses reduced oxidative gene expression, as expected. IDX exposure is thought to interfere with inflammation, oxidative stress, and tissue damage due to alterations in gene expression.

4.2.2 Hepatotoxicity and Renal toxicity

Pesticides are known to cause oxidative stress in the living system and the studies by Mudaraddi *et al*. (2012) [20] on liver oxidative stress induced by IDX in 90 days old male albino mice demonstrated its potential to cause oxidative damage. The liver oxidative stress by-products of lipid (Malonaldehyde) and protein (Protein carbonyl) were raised in mice treated with 18 and 24 mg/kg/day IDX, but GSH (Glutathione) and ascorbic acid were decreased. The liver enzymes SOD (Superoxide dismutase), Catalase, and GST (Gluthathione-s-transferase) were elevated in mice given 18 and 24 mg/kg/day of IDX, while oxidative stress by-products and enzymes in mice given 6 and 12 mg/kg/day of IDX were unchanged. On this basis, it was concluded that chronic IDX exposure is harmful to the liver.

Caballero *et al*. (2019) [11] studied effect of IDX on the cockroach *Periplaneta americana* by measuring the mortality rates at different time intervals of 24 h, 48 h and 72 hours after treatments. The toxicity of IDX alone, IDX combined with deltamethrin, or nano-encapsulated deltamethrin (LNC deltamethrin) was compared, and the results revealed that LNC-deltamethrin potentiated the effect of IDX. The study found that nano-encapsulation protected deltamethrin against esterase-induced enzymatic breakdown, resulting in improved IDX efficacy while lowering dosages and negative effects in non-target organisms. 50%, 25% and 10% of lethal dose of IDX in birds (98 mg/kg b.wt/day) administered to broilers (*Gallus domesticus*) revealed an increase in ALP, SGPT and AST which indicate hepatotoxicity and muscular damage. There was a significant increase in serum creatinine which suggest kidney damage induced by the insecticide (Kumar *et al*., 2013) [16]. IDX when administered as a pesticide mixture along with other chemicals alter the liver and kidney biomarkers even at minimal doses by depleting the enzymatic activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) while increasing the concentration of thiobarbituric acid reactive substances (TBARS) in these two organs, reflecting in the lipoperoxidation content (Sebti *et al*., 2023) [30].

The relative weight of the different organs viz. liver, kidney and brain were significantly elevated associated with IDX alone and in combination with abamectin treatments. The levels of serum aspartate aminotransferase (AST), gamma-glutamyltransferase (γ-GT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), glucose concentration and creatinine (Cre) were significantly increased while decrease in serum acetylcholinesterase (AChE) activity was observed due to tested insecticide treatments. The total protein and total antioxidant scavenging activity were also significantly decreased (Abdelrasoul, 2018) [1]. IDX residues were determined in the liver of rats by mass spectrometry method in which the highest residual level was seen on the 5th day of the LD50 1/10 treated rats and there was no residual pesticide on the liver after 40 days of the treatment (Parida *et al*., 2022) [25]. Chronic exposure of IDX to zebrafish, *Danio rerio* resulted in significant increase of catalase (CAT), glutamic oxalacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT). The metabolomics study revealed that IDX affected the metabolic pathways such as tricarboxylic acid (TCA) cycle and various amino acid metabolisms. Thus, IDX cause disturbance in metabolic pathway and a decline in detoxification ability of liver (Ma *et al*., 2023) [19].

4.2.3 Neurotoxicity

Wing *et al*. (1998) [35] chose lepidopteran larvae of *Manduca sexta* to study the hydrolytic metabolism of IDX. IDX (DPX-JW062) was orally administered and was rapidly cleaved to a decarbomethoxyllated metabolite (DCJW), as identified by HPLC and mass spectrometry. The resultant metabolite led to the appearance of neurotoxic symptoms. According to the tissue localization study conducted using fifth instar *Manduca sexta* larvae, the fat body and particularly the midgut are the most active tissues in catalyzing the conversion. The enzyme responsible for the conversion appears to have properties like an esterase/amidase. The US Environmental Protection Agency (EPA) [7] classified IDX as a "not likely" human carcinogen in a report issued in 2000. Neurotoxicity of the medication, on the other hand, was reported in multiple trials in both rats and mice, with symptoms such as weakness, head tilting, irregular gait, or movement, as well as an inability to stand. It was noted that some of these signs were observed at fatal doses. In utero or neonatal exposure to rat and rabbit proved no evidence of susceptibility to the drugs. It was also found that the compound gives a negative result for mutagenicity. The maximum tolerated oral dose (MTD) of IDX was found to be 500 mg/kg and 600 mg/kg in mice and rats, respectively. Several symptoms of toxicity including vigorous rolling, head tilt, hyperexcitation, salivation, intermittent clonic convulsions, restlessness, increase heart rate and respiration, loss of grip strength and biting behaviour were observed in toxicity studies (Shit *et al*., 2008) [32].

4.2.4 Effect on Haematopoietic system

Following IDX administration in rats, there was a significant rise in RBC counts, Hb content, Hct value, MCV, WBC counts, and platelet counts in comparison to the control group (p<0.05) (Hassan and Meligi, 2021) [15]. IDX caused a significant decrease in body weight while increasing the

relative organ weight of liver and spleen significantly in female Wistar rats fed 2.5% and 5% of Maximum Tolerated Dose (MTD), i.e., 3.1 mg/kg b.wt. and 6.2 mg/kg b.wt., respectively (Kumar and Kumar, 2016) [17]. IDX administration to male albino rats @600mg/kg b.wt induced pulmonary fibrosis with marked inflammation and neutrophil infiltration in the lung tissue (Ali *et al*., 2022) [2]. The house fly, *Musca domestica* and diamondback moth, *Plutella xylostella* showed resistance to IDX which suggest P450 involvement in the mechanism of resistance (Zhang *et al*., 2017; Shono *et al*., 2004) [33, 37].

IDX alone and in combination with abamectin treated rats showed significant and gradual decrease in body weight, haematocrit (%), platelets (PLT), erythrocyte counts (RBCs) and haemoglobin concentration (g/dL) (Abdelrasoul, 2018) [1]. Single dose acute toxicity study of the haematological parameters showed a decrease in leukocyte counts, haemoglobin content, and erythrocyte counts which suggests adverse effects on blood cells of mice (Shit *et al*., 2008) [32]. Toxicity studies of IDX reveals that it induces Heinz body formation and haemolytic anemia after oral administration in dog (Gwaltney, 2013) [13]. The reason behind this is suspected to be the formation of a metabolite N-hydroxyarylamine which causes oxidative damage to red blood cells.

4.2.5 Effect on the endocrine system

The plasma levels of T3 and T4 thyroid hormones decline, although not significantly, whereas TSH hormone levels increased significantly ($p<0.05$) in the IDX-treated rats compared to the control group (Hassan and Meligi, 2021) [15]. After 14 days of treating common carp *Cyprus carpio* with 1.5 ppm and 3 ppm of IDX, a decline in plasma T_3 levels were observed while plasma T_4 levels decreased after 21 days of treatment with 3 ppm of IDX (Ghelichpour *et al*., 2017) [10]. Oral administration of IDX to rats at the dose of 1/20 LD_{50} for 60 days results in a decrease in T3, FSH and progesterone while that of testosterone level increased in comparison to the control group (Nassar, 2016) [22].

4.2.6 Studies on the delivery forms of Indoxacarb

A recent study conducted by Yang *et al*. (2021) [36] was based on a safe delivery system of IDX. IDX was loaded into hollow mesoporous silica (HMS) nanoparticles. The prepared IDX loaded HMS-CD showed a high loading efficiency (26.42 percent w/w) according to the results of the test. The dual pH and amylase enzyme response characteristics were also outstanding. It was further demonstrated that IDX loaded HMS-CD nanoparticles' insecticidal activity against *Spodoptera frugiperda* was better when compared to the same dose of IDX emulsifiable concentrate. Furthermore, the toxicity of IDX loaded HMS-CD to zebrafish was reduced by more than 5-fold. Based on these findings, for sustainable control of pests and reduce harm to non-target organisms and the environment, insecticide delivery systems based on β-CD-anchored HMS nanoparticles could potentially be applied.

Reda *et al*. (2019) [27] worked on optimizing the biological activity of the pesticide to synthesize a product which was safe for use. For this, they determine various formulation types which have more impact on the efficiency of IDX against a lepidopteran insect called cotton leafworm, *Spodoptera littoralis*. Emulsifiable concentrate (EC), suspension concentrate (SC) and water dispersible granule (WG) are the three formulation types of IDX and were prepared in four concentrations each. The efficacy was evaluated against 3rd instar larvae of cotton leafworm *S. littoralis*. The mortality rate was relatively higher for the EC which indicated that it has more effect on the efficacy of IDX. They also estimated the spray solutions' physicochemical properties of these formulations and the result showed that the values of surface tension and pH of EC were lesser than SC and WG while EC has a higher viscosity and conductivity values than SC and WG. Thus, it was concluded that the EC formulation increased the efficacy of IDX much more than the other two formulations.

IDX-loaded nanoparticles (carbon dots-embedded fluorescent mesoporous silica nanoparticles) was reported to have better insecticidal activity against lepidopteran pest *P. xylostella* than the technical IDX applied under similar doses of active ingredient. Furthermore, this IDX loaded nanoparticle suppressed the activity of detoxification enzyme P450 to a greater extent (Bilal *et al*., 2020) [5].

5. Figures

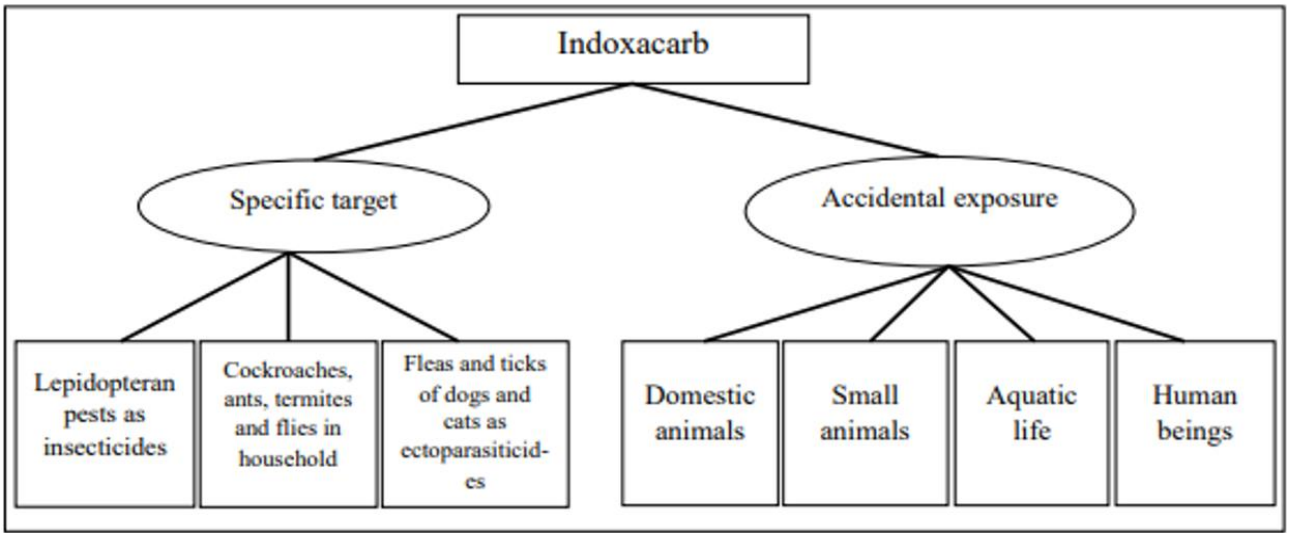

Fig 1: Specific and accidental exposure to Indoxacarb

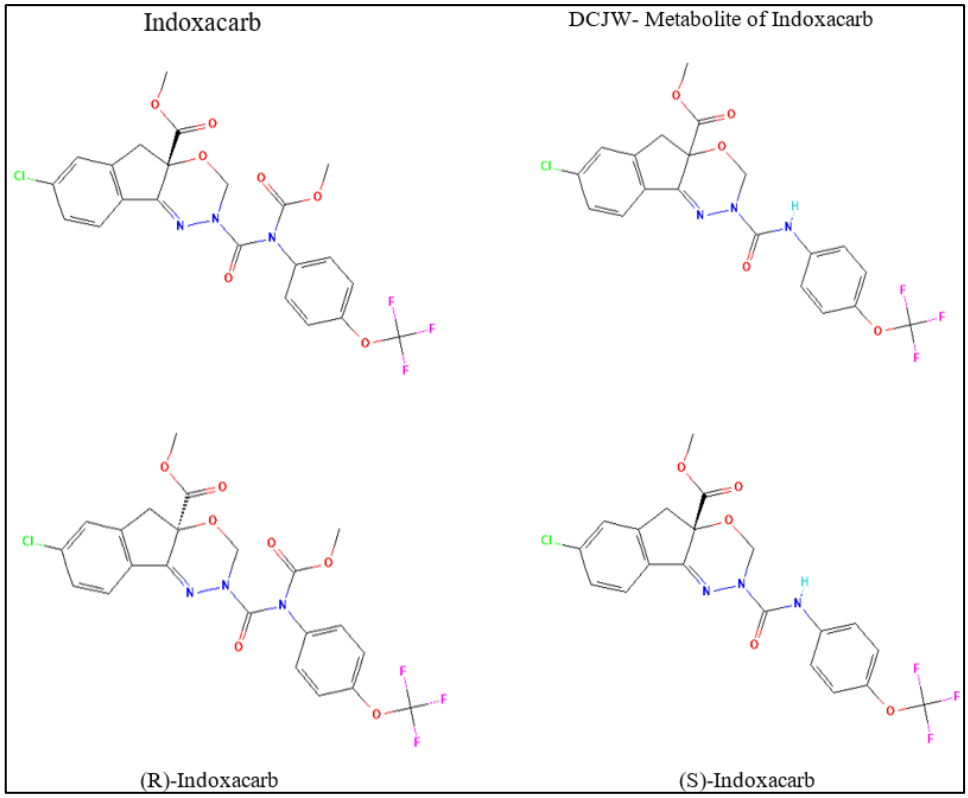

Fig 2: Molecular structure of Indoxacarb, its metabolite and different enantiomers

6. Conclusion

Indoxacarb has fewer detrimental effects on one's health and the environment. It is moderate to severely harmful to aquatic life and less dangerous to mammals. However, there has been several reports on the toxic effects of IDX exposure. Its effect on the respiratory system was observed by a decrease in oxygen consumption *in vitro*. The metabolite DCJW seems to be more potent in blocking the sodium channel of insects and cause neurotoxicity as evidenced by certain neurotoxic symptoms. It is reported to be non-genotoxic, non-carcinogenic and does not induce mutation although it is shown to lower the cellular viability in *in vitro* studies. IDX causes immunotoxicity by increasing certain inflammatory cytokine gene expressions and also induces lymphocytopenia. IDX is toxic to vital organs like liver and kidney and induces oxidative stress by altering the activity of antioxidant enzymes. It also effects the haematopoietic system as well as the endocrine system by changing the blood profile and the level of certain hormones, respectively. On the contrary, it has been widely used as an insecticide to control bollworms in cotton, pod-borers in pulses, pests in vegetables, especially cabbage and cauliflower, and forage crops. As a result, animals and humans are more likely to be exposed to this poison. In order to utilise indoxacarb wisely, it is important to understand the harmful effects of this insecticide on non-target species, and familiarize with safe use pesticides as certain studies have shown that it is hazardous to vertebrates.

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