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Carbaryl and Human Health: A Review

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ABSTRACT

Carbaryl (1-naphthalenylmethylcarbamate) is one of the most frequently used carbamate insecticides. Carbaryl has elicited some serious carcinogenic activity in the chronic rodent studies and has also been found to cause tumors in the liver. Though carbaryl is relatively safe to mammals, but carbaryl causes damage to hepatocytes. It has other biochemical effects, as it reacts with reduced glutathione and probably directly with other accessible protein hydroxyl and sulphydryl groups or indirectly through reactions involving the glutathione conjugate. In mammals, carbaryl inhibits acetylcholinesterase causing several neural problems. Some recent reports suggest it can bind human melatonin receptors exerting serious implications on human health. Here in this review an attempt has been made to summarise carbaryl's mode of action and its ill effects on human health.

INTRODUCTION:

Carbamate insecticides have a variety of chemical structures, but all derive from carbamic acid, the majority being *N*-methylcarbamates. Carbaryl (1-naphthalenylmethylcarbamate, Molecular weight-weight- 201g) is one of the most frequently used carbamate insecticides and widely used for the control of a variety of pests on fruit, vegetables, forage, cotton and many other crops, as well as on poultry, livestock and pets (1). It is available as wettable powders, pellets, granules, dusts, suspensions and even solutions.

Carbaryl has a low vapor pressure, 1.17 x 10^{-6} mmHg and is not readily volatilized into the air. A low Henry's law constant, 2.74 x 10^{-9} atm m^3g.mol^{-1} suggests that carbaryl has low potential to volatilize from aqueous solution (2). It might be found in the atmosphere associated with air-borne particulates or as spray drift but should not be over a large area. If existing in air, carbaryl tends to react with hydroxyl radical in the ambient atmosphere (3). Overall, carbaryl is not persistent in soil. It can be degraded through hydrolysis, photolysis as well as by microorganisms. The photodegradation of carbaryl was investigated on soil under artificial sunlight for a total of 30 days (4). In water, the compound degrades rapidly at pH 7 and 9 at 25^0C, with half-lives of approximately 10~17 days and 3 hours, respectively (5). In acidic water, carbaryl is rather stable with a half-life of more than 1500 days at 270C (6). Carbaryl does not readily volatize into the atmosphere and it is unlikely to volatize from water to air. Carbaryl moderately binds to soil and has potential to leach to groundwater (7). It is not persistent in soil since it can be hydrolyzed, photodegraded, oxidized, degraded by microbes. In alkaline or neutral water, hydrolysis is the major degradation route for carbaryl, with half-lives ranging from a few hours to many days. The current Guideline Value for carbaryl in drinking water is 0.005 mg/L. Carbaryl is one

of the most important carbamate insecticides and has been used for over 30 years to control a wide range of pests, particularly in developing countries. The absorption, excretion and toxicokinetics of carbaryl are typical of the carbamate class. Carbaryl is extensively absorbed by the oral route and excreted rapidly in the urine by humans and experimental animals except dogs, in which the faeces is also a significant route of excretion. There is little tendency for carbaryl or its metabolites to accumulate in body tissues, even after subchronic administration. Carbaryl induces the hepatic mixed function oxidase system in mice. The toxic effects of carbaryl related to reproductive toxicology (8-12) and genetic toxicology (13-15) have also been extensively investigated. Carbaryl is remarkable for its carcinogenic activity in the chronic rodent studies by Hamada (16,17), having caused tumours of the thyroid, urinary bladder and liver in rats, and kidney, liver and vascular system in mice. Carbaryl- induced genotoxic effects have been reported by in vitro studies as mitotic aberrations in V79 Chinese hamster fibroblasts (15) and sister-chromatid exchanges in V79 Chinese hamster cells (14). Grover et al. (18) described carbaryl as a selective genotoxicant because it could induce both clastogenic and physiological types of chromosomal aberration. Pesticides or Insecticides are not always selective for their intended target species, and adverse health effects can occur in non target species, including humans. They play a major role in the control of insect pests, particularly in developing countries. All of the chemical insecticides in use today are mostly neurotoxicants, and act by poisoning the nervous systems of the target organisms. The central nervous system of insects is highly developed and not unlike that of mammals, and the peripheral nervous system, though less complex, also presents striking similarities (19). Thus, insecticides are most often not species-selective with regard to targets of toxicity, and mammals, including humans, are highly sensitive to their toxicity. In the general population and in occupationally exposed workers, a primary concern relates to a possible association between pesticide exposure and increased risk of cancer (20,21).

There are several cases of human poisoning associated with exposure to various carbamates, in particular carbaryl (22) and propoxur (23). They present different degrees of acute oral toxicity, ranging from moderate to low toxicity such as carbaryl, to extremely high toxicity, such as aldicarb. In population-based studies, some epidemiologic and occupational studies found that carbaryl exposure had correlation with adverse reproductive outcomes such as infertility, pregnancy loss, and stillbirth (8, 11). However, the potential mechanisms of these toxic effects are not clear. Recently, Meeker et al. (24) suggested the relationship between carbaryl exposure and increased DNA damage in human sperm. Human carbaryl exposures from pesticide manufacturing (8,11,12), crop-dusting (10) and daily-life contacting (9,25) are common.

MODE OF ACTION:

Carbaryl is an insecticide which acts primarily by inhibiting acetylcholinesterase by carbamoylation of a serine hydroxyl group at the active site (26). Like most carbamates, carbaryl acts as an inhibitor to cholinesterase, one of many important enzymes in the nervous systems of humans, vertebrates and insects (27). A specific cholinesterase enzyme, acetylcholinesterase (AChE), plays an important role in breaking down the acetylcholine (Ach), which is the synaptic mediator of nerve impulses in the 4 nervous systems of mammals and insects (28). The presence of cholinesterase inhibiting

pesticides, such as carbaryl, prevents AChE from breaking down acetylcholine and results in high concentration of Ach in the nervous system. As a result, the continuous stimulation of the muscle leads to uncontrolled, rapid movement of some muscles, paralysis, convulsions and even death.

phosphorylation. Carbaryl causes a reversible block in metaphase, spindle microtubule depolymerization, displacement of chromosomes to the periphery of the cell and, concomitant to this, a remarkable progression of the cytoplasmic changes typical of anaphase and telophase (13, 15, 33).

Though carbaryl is relatively safe to mammals, 10 M and 1mM carbaryl causes damage to

Signs and Symptoms of Acute Poisoning with Anticholinesterase Compounds	
AFFECTED SITES	**SYMPTOMS / MANIFESTATIONS**
Exocrine glands	Increased salivation, lacrimation, perspiration
Eyes	Miosis, blurred vision
Gastrointestinal tract	Abdominal cramps, vomiting, diarrhea
Respiratory tract	Increased bronchial secretion, bronchoconstriction
Bladder	Urinary frequency, incontinence
Cardiovascular system	Bradycardia, hypotension, Tachycardia, transient hypertension
Skeletal muscles	Muscle fasciculations, twitching, cramps, generalized weakness, flaccid paralysis
Central nervous system	Dizziness, lethargy, fatigue, headache, mental confusion, depression of respiratory centers, convulsions, coma

In an evaluation of humoral immunity following a 2-week exposure to carbaryl in rats, suppression of the IgM PFC response to sRBC was observed following inhalation exposure, but not oral or dermal exposure (29).

The compound also has other biochemical effects, as it reacts with reduced glutathione and probably directly with other accessible protein hydroxyl and sulphydryl groups (13,30,31) or indirectly through reactions involving the glutathione conjugate (32). During carbamoylation the aromatic part of carbaryl will be released in the form of 1-naphthol, which is an uncoupler of oxidative

hepatocytes (34). Apparently less harmful carbaryl has some serious effects on human, as evidenced by morphologic abnormalities and genotoxic defects of spermatozoa, DNA breakage and chromosomal aberrations (35). Amer et al. (36) found carbamate pesticides to inhibit antioxidant enzyme (SOD and GPx) activities in human. Eraslan et al. (37) reported functional disorder of rat liver following carbaryl treatment. Delescluse et al. (38) also suggested that carbaryl provoked a strong DNA-damaging activity in the human lymphoblastoid cell line.

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REACTIVE OXYGEN SPECIES (ROS) :

Reactive oxygen species (ROS) is a combined term that basically expresses oxygen-derived free radicals e.g. superoxide anion (O_2•), hydroxyl (HO•), peroxyl (RO_2•), and alkoxyl (RO•) radicals. Moreover some O_2-derived nonradical species such as hydrogen peroxide (H_2O_2) is also a part of it (39). ROS are transient species formed during the normal course of cellular metabolism and xenobiotic exposure. Depending on the concentration of ROS, it can be beneficial or harmful to cells and tissues. Elevated levels of highly reactive ROS damage cellular macromolecules including proteins, lipids, and mitochondrial and nuclear DNA, and promote cell death. These biological perturbations often result in the propagation of more ROS molecules and lipid peroxides. The end result of this cascade is cellular dysfunction and/or death. Similarly, electrophilic compounds can interfere with normal cell function directly by binding to cell structures or indirectly by producing ROS. Cells possess defense systems that provide protection against oxidative stress and ameliorate oxidative injury (ROS) (40) (Fig.1.).

GLUTATHIONE:

Endogenous antioxidants such as glutathione (GSH) can scavenge and inactivate ROS, thereby restoring cellular homeostasis. The tripeptide (L-gglutamyl-L-cysteinyl-glycine) glutathione (GSH) is the major antioxidant and redox regulator in cells that is important in combating oxidation of cellular constituents. It is the most abundant nonprotein thiol representing about 80-90% of all non-protein thiol (NPSH) of a cell (41) (Fig.2.). It is a water phase orthomolecule found widely distributed in animal tissues, plants, and microorganisms (42). Cells spend a great deal of energy to maintain high levels of intracellular reduced GSH and its high electron -donating capacity (high negative redox potential) in turn helps to keep proteins in a reduced state (43). Under physiological conditions, GSSG reductase maintains more than 98% of intracellular GSH in the reduced, thiol form (GSH). The rest is present within the cell as mixed disulfides (mainly GS-S-protein), as the disulfide (GSSG), and as thioethers (44). The importance of glutathione is reflected through (*a*) the maintenance of protein structure and function by reducing the disulfide linkages of proteins, (*b*) the regulation of protein synthesis and degradation, (*c*) the maintenance of immune function, (*d*) protection against oxidative damage, and (*e*) detoxification of reactive chemicals. Therefore a reduction in the intracellular GSH level will reduce the cell's functional capabilities and in most severe deficiency leads even to cell death (45).

A general mechanism for the detoxication of electrophilic toxicants is conjugation with the thiol nucleophile glutathione (46). This reaction may occur spontaneously or can be facilitated by glutathione *S*-transferases. This is followed by the transfer of the glutamate by γ-glutamyl transpeptidase, by loss of glycine through cysteinyl glycinase and finally by the acetylation of the cysteine amino group (47).

GSH S-TRANSFERASE :

Ellectrophiles (E) + GSH ⟶ GS-E

Metal ions readily react with and are detoxicated by glutathione. Specific mechanisms, for the detoxication of electrophilic chemicals include epoxide hydrolase-catalyzed biotransformation of epoxides and arene oxides to diols and dihydrodiols, respectively, and carboxylesterase catalyzed hydrolysis of organophosphate ester pesticides. GSH also

reacts with metals nonenzymatically like other thiols (48-50). Metals catalyze auto-oxidation of thiols including GSH, at alkaline pH with a concomitant production of superoxide radicals. The overall reaction between GSH and metal is as follows (51):

$$6\ GSH + O_2 + 2\ Me^{+2} \longrightarrow GSSG + 2\ GS\text{-}Me\text{-}SG + H_2O_2 + 4H^+$$

This reaction is a key one leading to metal detoxication as GSH acts as a chelate and transporter of a number of intracellular substances across the cell membrane. The GSH-metal chelates thus formed are excreted in the bile (52).

ROS AND SIGNALING TRANSDUCTION:

Although ROS have been demonstrated to be involved in many signal transduction pathways the molecular targets are not yet precisely defined. In addition, there is a select set of genes encoding detoxifying enzymes, antioxidant proteins, and stress proteins that can remove compounds and/or intermediates capable of generating ROS. Induction of these genes is an adaptive defense to counteract oxidative stress. Superoxide radicals and hydrogen peroxide play an important role as regulatory mediators in physiological signaling processes. Oxidative stress occurs if either the production of ROS is abnormally increased or the antioxidant concentration is decreased. Oxidative stress can lead to tissue damage and to the dysregulation of redox-sensitive signaling pathways.

The addition of extracellular ROS has been demonstrated to activate mitogen-activated protein kinase (MAPK) pathways in a number of preparations. This holds true for the extracellular regulated kinase 1/2 (ERK1/2) pathway as well as for the c-Jun N-terminal kinase (JNK) and p38 MAPK pathways. In contrast to the ERK1/2 pathway which is involved in cell differentiation and proliferation, the JNK and p38 pathways are mainly activated by stress stimuli including oxidative stress. Another very important transcription factor Nrf2 is of particular importance to the regulation of detoxifying and antioxidant genes. This is one of multiple cellular redox status sensors. Nrf2 binds the promoters of these genes through specific responsive elements, regulating both their constitutive and inducible expression (53-55).

CARBARYL HINDERS HUMAN REPRODUCTIVE SYSTEM:

Meeker et al. (24) assessed semen quality and reported that an interquartile range increase in carbaryl metabolite levels in urine is associated with a 4% decrease in sperm motility which can lead to increase in the number of sub-fertile men. They further suggested a relationship between carbaryl exposure and increased DNA damage in human sperm.

CARBAMATE INSECTICIDES TARGET HUMAN MELATONIN RECEPTORS

Rajnarayanan and his group have recently showed Carbaryl can bind to Human Melatonin Receptors hMT1 and hMT2 (56). It is novel mechanism by which carbaryl and carbofuran insecticides of carbamate class may adversely impact human health by disrupting the homeostatic balance of key regulatory processes by directly binding to melatonin receptors. Subsequently, this can alter the melatonin mediated signaling causing serious health issues in human. Apart from direct binding to human melatonin receptors, carbaryl and carbofuran are also reported to alter the metabolism of serotonin which is a precursor of melatonin (*57*).

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CARBAMATE INDUCED TYPE 2 DIABETES

Organochlorines and organophosphorus are the most studied insecticides which bears strong correlation with obesity and/or type 2 diabetes in humans and rodents (58). Insecticide like carbamates has also been reported to develop obesity and/or type 2 diabetes as well. Liver, as one of the principal organs in regulation of glucose homeostasis, Carbaryl has shown to damage normal liver function. It influences acetylcholine level or its receptors by disrupting acetylcholine esterase it can all potentially stimulate insulin release from the pancreas (59). Like wise, carbamate insecticide reported to cause acute pancreatitis, which potentially influence insulin secretion in human and animal (60).

EFFECT ON IMMUNE SYSTEM:

In vivo studies illustrate carbamate pesticides are immunomodulator that can make the host immunocompromised (61). It is well documented that carbamate induce apoptosis in human natural killer cells it has also been reported that carbamate can induce apoptosis in human T lymphocytes (62). Carbaryl dis-orients the whole immune system primarily by induction of mutations in genes transcribing immunoregulatory factors, direct immunotoxicity, endocrine disruption and inhibition of Acetyl choline esterases. Report suggests altered immune system render different types of cancers, allergies, autoimmune and infectious diseases (63).

CONCLUSION:

Although many country has banned Carbaryl but still several nation is continuing the use of carbamate insecticides for its low toxicity in comparison to organo-chlorines or phosphates. Several reports suggest even low level chronic exposure of carbaryl poses serious risk on human health. Carbamate insecticides, used on a wide range of crops, have shown evidence of carcinogenicity with increased risks of CNS tumours. Oxidative stress is the main mechanism by which carbaryl causes alteration in biological system. Carbaryl has been reported to disrupt endocrine system, reproductive system, increase susceptibility to immunotoxicity and infectious diseases.

Here we have discussed direct effect of carbaryl on human health but a few indirect effects have raised serious concerns. Indiscriminate use of carbamate insecticides in malaria management has started developing resistances within the pests with the fear that such resistance could severely disrupt malaria control in the society. In view of the long term and serious adverse effect posed by carbaryl, we have to be more cautious and rational with the use of carbamate pesticides in general.

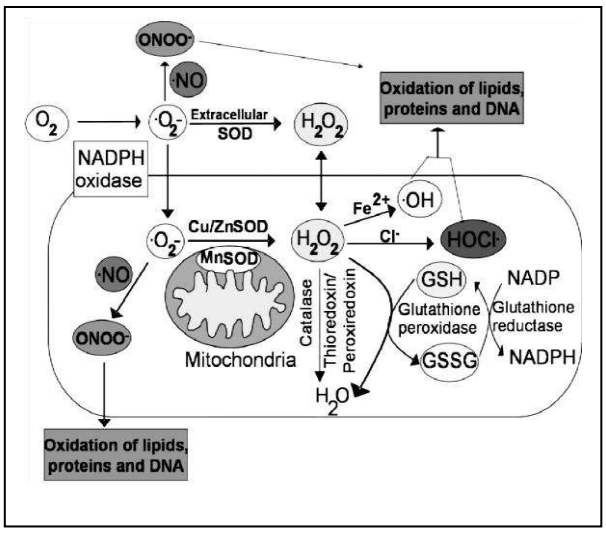

Fig.1. Schematic representation of the major pathways involved in the intracellular production of reactive oxygen/nitrogen species (40).

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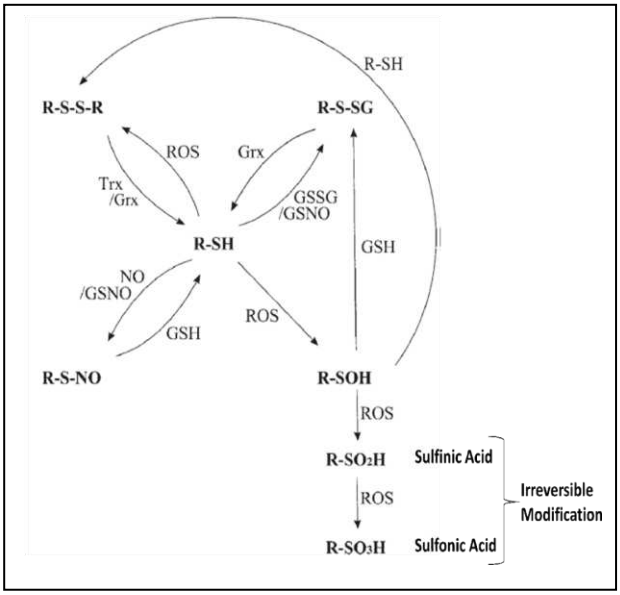

Fig.2. Stable modifications of protein thiol groups and their interconversion. (41).

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