Dichlorvos toxicity: 
A public health perspective

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ABSTRACT
Pesticides are used in agriculture and in domestic pest control. Dichlorvos, an organophosphate, is a predominant pesticide used in domestic insect control in developing countries. Acute and prolonged exposure may lead to death, genotoxic, neurological, reproductive, carcinogenic, immunological, hepatic, renal, respiratory, metabolic, dermal and other systemic effects. Its toxicity is due to the ability of the compound to inhibit acetyl cholinesterase at cholinergic junction of the nervous system. This study is a review of the toxicological effects of dichlorvos in a public health perspective.

KEY WORDS: dichlorvos; organophosphate; pesticide; insecticide; acetyl cholinesterase; toxicity

Introduction
Dichlorvos, also known as DDVP (2,2-dichlorovinyl dimethyl phosphate is an organophosphate insecticide cum pesticide (USEPA, 2007). It is traded under names such as DDVP, Dedevap, Nogos, Nuvan, Phosvit, Vapona, Sniper and Daksh (Owoeye et al., 2012; Meister 1992). Dichlorvos (Figure 1) has the molecular formulation C4H7Cl2O3P, molecular weight of 220.98, vapor pressure of 1.2×10−2 mmHg at 20 °C, and density of 1.415 g/ml at 25 °C (Budavari, 1998). It is classified by the WHO as a class 1B, "highly hazardous" chemical (WHO, 1992).

Dichlorvos is usually used as a household and agricultural pesticide. It is the most commonly used organophosphate pesticide in developing countries (Binukumar and Gill, 2010). It is also used as an anthelminthic agent on dogs, horses and swine (USEPA, 1994). Dichlorvos has been used in fish farming to eradicate crustacean ectoparasites (Varo et al., 2003). It has been in use since the early 1960s and has been the subject of many toxicity studies (Durkin & Follansbee, 2004). The present study is an attempt to review the public health concerns of dichlorvos toxicity.

Production of dichlorvos
One method of production of dichlorvos is the dehydrochlorination of trichlorfon in aqueous alkali at 40–50 °C (WHO, 1989). It is also produced commercially by a reaction of trimethyl phosphate and chloral (Sittig, 1980).

Legislations/regulations of dichlorvos
Dichlorvos present a legislative conundrum as the body of experimental result relating to its safety and non-safety continues to expand (Mennear, 1998). Different countries view both sides of the argument differently while considering the economic implications.

Dichlorvos has been reviewed under the Biological Product Directive (BPD) and the decision not to include dichlorvos in Annex 1/1A of the BDP commission approved list of active substances for use in biocidal products in Europe was reached. This implies that insecticide products containing dichlorvos should no longer be placed on the market with effect from November 1, 2012 (EU, 2012). This decision was reiterated later in 2013 (EU, 2013). However, there is significant variability in its use across the European Union (EU), with some member states not using the substance at all and others still having a range of uses (EC, 2011).

Following the review of dichlorvos in the United Kingdom (UK), decision was taken on suspension of sale of all insecticide products containing dichlorvos in 2002.
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(2011), following recommendation of the Advisory Committee on Pesticide (HSE, 2002).

Dichlorvos status in some countries that has restrictions or ban are listed in Table 1. However, there have been non-governmental interventions in the form of conventions: the Stockholm convention on persistent organic pollutants that aimed at protecting human health and the environment from persistent organic pollutants; the Rotterdam Convention that takes the obligation of early warning about bans and restrictions of pesticides that has been banned by two countries in two regions (Imig, 2010).

Environmental degradation

The initial release of dichlorvos is mostly into air. In contact with water, hydrolysis reaction becomes the major mechanism for degradation (Faust & Suffet, 1996; Lamoteaux, 1978). In the environment, abiotic degradation via hydrolysis is the major transformation process.

Dichlorvos does not strongly absorb ultraviolet light above 240 nm (Howard, 1991; Gore et al., 1971) and hence it is unlikely to be photolyzed in the atmosphere. On theoretical consideration, dichlorvos is likely to be degraded in the air from free radicals, such as hydroxyl groups or ozone.

Dichlorvos is highly soluble in water and has the tendency to remain in solution with very little tendency to sorb to sediment. In solution, dichlorvos becomes subject to both abiotic and biological degradation, with the predominant mechanism being hydrolysis. Dichlorvos is hydrolyzed to dichloroethanol, dichloroacetaldehyde, dichloroacetic acid, dimethylphosphate and dimethylphosphoric acid (WHO, 1989). The degradation is more rapid in alkaline pH (Lamoteaux, 1978) and high temperature (Faust, 1996). A study by Lartiges and Garrigues (Lieberman & Alexander, 1983) investigated the degradation of dichlorvos in different types of water under different environmental conditions. The study reported that in winter temperature, dichlorvos was still present in filtered water (pH 6.1) after 180 days; residues in river water (pH 7.3) and filtered river water (pH 7.3) disappeared after 81 days; residues in sea water (pH 8.1) disappeared after 34 days. In summer, dichlorvos residues disappeared after 81, 55, 34 and 180 days for filtered water, river water, filtered river water and sea water, respectively. Microorganisms found in sewage sludges apparently can degrade dichlorvos which may require acclimation. However, the rate of degradation is slower than abiotic degradation (Lieberman & Alexander, 1983).

In soils harboring good quality of moisture, hydrolysis reaction similar to those in aqueous solutions are expected to occur (PIP, 1993). However, half-life (first-order kinetics) of 17 days in soil have been reported (Hayes, 1990), though the authors were not specific of the soil type. Hayes and Laws (1990) reported an average half-life of 16 days in silty clay soil (pH 5.5) and sandy clay soil (pH 6.9) irrespective of the soil type. More so, Lamoreaux (1978) investigated the rate of dichlorvos in Houston Black clay soil for 10 days at room temperature of 26°C. They reported that the fate of dichlorvos degradation in the soil was directly related to the presence of bacterium Bacillus cereus, the pH of the soil perfusion system and the extent of dichlorvos adsorption. The study reported more rapid degradation in the presence of B. cereus (3.9 days half-life) as against 10 days for sterile soil. Hydrolysis and other non-biological processes accounted for 70% of total degradation of dichlorvos, while bacteria degradation accounted only for 30% in the soil perfusion system (Lamoteaux, 1978). The proposed pathway for the breakdown of dichlorvos in the soil and water/sediment system is shown in Figure 2 as adapted from APVAM (2008).

Table 1. Dichlorvos status in some countries.

| Country     | Status   | Reference        |
|-------------|----------|------------------|
| Sri Lanka   | Banned   | Eddleston et al., 2003 |
| USA         | Restricted | ICAR-RC, 2015 |
| Kuwait      | Restricted | ICAR-RC, 2015 |
| Korea       | Restricted | ICAR-RC, 2015 |
| Bangladesh  | Banned   | FAO-UN, 2013    |
| Cambodia    | Banned   | FAO-UN, 2013    |
| Vietnam     | Restricted | FAO-UN, 2013 |
| Australia   | Restricted | APVMA, 2011    |
| Canada      | Restricted | Health Canada, 2011 |
| Denmark     | Banned   | European Commission, 2011 |

Metabolic fate of dichlorvos in human and other mammals

Of the organophosphates, dichlorvos is distinct for its rapid metabolism and excretion by mammals. Dichlorvos was not detected in the blood of mice, rats and humans after exposure at atmospheric concentration of up to 17 times that normally reached for insect control in homes. This rapid disappearance is due to the presence of degrading enzymes in tissues and blood plasma (Hayes & Laws, 1990; Hayes, 1982). Dichlorvos does not accumulate in body tissues and has not been detected in the milk of cow or rat even at doses capable of producing symptoms of poisoning (Hayes & Laws, 1990).

Figure 1. Structural formula of dichlorvos.

Figure 2. The proposed pathway for the breakdown of dichlorvos in the soil and water/sediment system as adapted from APVAM (2008).
The liver is the major site of dichlorvos detoxification (Gains et al., 1996; Casida, 1966). However, blood, kidney, lung, spleen metabolize dichlorvos mostly to dimethyl phosphate. Other metabolites are desmethyl dichlorvos, monomethyl phosphate, and inorganic phosphate (Loeffler et al., 1976). The pathway of metabolism of dichlorvos is shown in Figure 3 as adapted from Wright et al. (1979).

Studies have reported the metabolism of dichlorvos in humans (Hutson & Hoadley, 1972a), rats (Casida et al., 1962; Hutson & Hoadley, 1972b), mice (Hutson & Hoadley, 1972b), Syrian hamsters (Hutson & Hoadley, 1972a), pigs (Loeffler et al., 1976), goats (Casida et al., 1962) and cows (Casida et al., 1962). The submissions of these studies showed that dichlorvos metabolism is generally similar in different species of mammals with minor difference in quantification and in relation of the rate of the metabolic pathway (ATSDR, 1997). Two enzymatic mechanisms exist for the breakdown of dichlorvos; the glutathione independent mechanism catalyzed by “A” type esterases that produces dimethyl phosphate and dichloroacetaldehyde (Wright et al., 1979) and the glutathione dependent mechanism that produces desmethyl dichlorvos and S-methyl glutathione. Subsequent breakdown of desmethyl dichlorvos to dichloroacetaldehyde and monomethyl phosphate is also catalyzed by “A” esterases (Wright et al., 1979). S-methyl-glutathione is broken down to methylmercapturic acid and excreted in urine of the subject animal.

**Mechanism of toxicity**

Dichlorvos exerts its toxic effect by irreversibly inhibiting neural acetylcholinesterase (Wang et al., 2004). The inhibition provokes the accumulation of acetylcholine in synapses with disruption of nerve function (Wang et al., 2004). The consequences of the altered cholinergic neurotransmission in the parasympathetic autonomic nervous system includes perspiration, nausea, lacrimation, vomiting, diarrhea, excessive bronchial secretion or even death (ATSDR, 1997). Effects on motor nerve fibers in skeletal muscles can include muscle cramps, muscle fasciculation, muscle weakness and flaccidity. The cholinergic effect in the central nervous system results in drowsiness, fatigue, mental confusion, headache, convulsions, coma and even death (ATSDR, 1997).

However, the nervous system can tolerate a certain amount of acetylcholinesterase inhibition without overt toxic effects. In humans and mammals, toxic signs were not generally seen until at least 20% acetylcholinesterase was inhibited (Ecobichon, 1991).
Figure 3: Mammalian pathway of metabolism of Dichlorvos (Adapted from Wright et al., 1979)
Routes of exposure

One of the routes of exposure of dichlorvos is inhalation. People living near hazardous waste sites containing dichlorvos or those using it as domestic pesticide could be potentially exposed to its inhalation. Another possible route of exposure is skin contact with soil contaminated with dichlorvos or body splash. There is also possible oral exposure by ingesting food items contaminated with dichlorvos or direct ingestion (Gallo and Lawryk, 1991; USPHS, 1995).

Health effects

Exposure to dichlorvos could result in acute or chronic toxicity. Because dichlorvos is volatile, inhalation is the most common route of acute toxicity. Acute illness from dichlorvos is usually limited to cholinesterase inhibition (Casida et al., 1962). Repeated or prolonged exposure to dichlorvos may result in the same effect as acute exposure including delayed symptoms. The specific toxicity effects are discussed.

Death

There was no available study on death via inhalation of dichlorvos by humans. However, Hayes (1982) documented the case of a woman who died a day after ingestion of dichlorvos. The second report was that of a 19-month-old girl that died following ingestion of a cake-like bait that contained dichlorvos (Hayes, 1982). Moreover, it was reported that two pesticide workers in Costa Rica died after spilling a dichlorvos containing insecticide on their skin without washing it off properly (Hayes, 1982).

Earlier animal studies reported death within 7 to 62 hours after exposure to air saturated with dichlorvos for rats (Durham et al., 1957). Thorpe and Colleagues (1972) reported death of pregnant rabbits after inhalation of dichlorvos for 28 days at 4 mg/m³ and 6.25 mg/m³. Acute toxicity studies reported LD₅₀ of 50 mg/kg (Durham et al., 1957), 97.5 mg/kg (Keda et al., 1990), 133 mg/kg (Haley et al., 1975) and 139 mg/kg (Haley et al., 1975) for female Sherman rats, male fisher rats, female mice, and male mice, respectively. Aquatic studies have reported LC₅₀ values ranging from 0.2 to 12 mg/L for freshwater and estuarine fish (Suchismita, 2013).

Genotoxic effect

In vitro genotoxicity of dichlorvos has been reported. Dichlorvos has been reported not to be genotoxic in vivo in animal studies (Nazam & Shaikh, 2013; Dean & Thorpe, 1972). However, in an in vitro study, Fiore and colleagues (2013) reported disruption of mitotic division, production of mitotic arrest and chromosome aneuploidy/polyplody in the proliferation of cell population in human cell culture by dichlorvos. The study demonstrated that the major effect of dichlorvos on mitosis spindles with monopolar microtubule arrays that are associated with hypercondensed chromosomes and pyknotic chromatin masses.

Neurological effect

Dichlorvos exerts its toxic effects in humans and animals by inhibiting neural acetylcholinesterase (ATSDR, 1997). Neurological effects have been reported in a number of animal studies following acute oral exposure with little information on humans. Luiz and Colleagues (2002) reported a case of organophosphate-induced delayed neuropathy of two weeks later in a 39-year-old lady who drank large amount of a dichlorvos based insecticide. In an animal study, Aditya et al. (2012) reported activation induced apoptotic cell death in primary rat microglia. Activation of the microglia cells resulted in microgliosis manifested by increased damage in the affected regions. The study reported that the microglial cells undergo cell death after 48 hours of dichlorvos treatment. In another study, Binukumar et al., (2010) reported Nigrostriatal neuronal death following chronic exposure of 2.5 mg/kg/daily of dichlorvos in rat. The study submitted that chronic exposure to dichlorvos causes nigrostriatal dopaminergic degeneration accompanied by 60–70% reduction in striatal dopamine and tyrosine hydrolase levels. In an earlier study, using male Fischer 344 rats exposed to dichlorvos via olive oil gavage, an LD₅₀ study showed signs of severe cholinergic stimulation including salivation, tremors, lacrimation, fasciculation, irregular respiration and prostration (Ikeda et al., 1990).

Reproductive effect

There is no available literature on the reproductive effect of dichlorvos in humans. However, a study on the effects of dichlorvos on fertility of male mice via intraperitoneal injection reported significant decrease in sperm number and increase in sperm abnormalities (Faris, 2008). In another study, Ezeji and Colleagues (2015) reported significant reduction in testosterone levels of adult male rats fed water contaminated with dichlorvos. The study also reported levels of distortions in the cells of the seminiferous levels as well as hypertrophy of the spermatogonia cells (Ezeji et al., 2015).

Developmental effect

There is no literature on developmental effect of dichlorvos following exposure on humans. However, several animal studies on developmental effects of dichlorvos have been reported. Sisman (2010) examined the effect of varying concentrations of dichlorvos on the embryonic development of zebrafish. The study reported developmental abnormalities such as lack of blood flow, cardiac edema, delayed hatching and vertebra malformations in embryos and larvae. Another study by Thorpe and Colleagues (Thorpe et al., 1972) investigated developmental effects of dichlorvos via inhalation in fifteen (15) pregnant E rats within their twenty-day gestational period. The study reported stillbirths, resorption sites, skeletal defects, gastroschisis and other external malformations.
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Carcinogenic effect
There is no literature on the carcinogenic effects on humans. Several animal studies, including that of Wang and Colleagues (2013), examined the risk assessment of mouse gastric tissue cancer induced by dichlorvos and dimethoate using varying doses on male Kunming mice. The study reported upregulation of p16, BCL-2 and C-myc genes in mouse gastric tissue in the orally administered 40mg/kg/day dose category. Hence the authors submitted that mouse gastric tissues exposed to high doses of dichlorvos in the long term have the potential to become cancerous (Wang et al., 2013). In an earlier study (NTP, 1989) with 50 Fischer 344 rats using oral gavage in corn oil, the authors reported significant neoplasms in the pancreas and the hematopoietic system of the male rats and the mammary gland of the female rats; mononuclear cell leukemia and pancreatic adenoma increased in the male, benign mammary tumors increased in females (NTP, 1989; Ishmael et al., 2006). Moreover, the same study reported significant positive trend of forestomach carcinoma and squamous cell papilloma in female mice.

Immunological effect
There is evidence from occupational exposures that dichlorvos has the potential to cause skin sensitization. Human diagnostic patch tests of occupational flower growers with a history of pesticide dermatitis have shown an allergic contact dermatitis response to dichlorvos (NIOSH, 2017; Ueda et al., 1994; Fuji, 1985). In an animal study, Desi et al. (1980) studied the effect of daily oral administration of LD_{50} 1/40, 1/20, 1/10 dichlorvos in male rabbits (2.0–2.5 kg body weight) after vaccination with Salmonella typhi. The study reported a dose-dependent fall in the serum antibody titer of the treated animals in contrast with the control group.

Hepatic effect
Zhao et al., (2015) reported a case of dichlorvos induced autoimmune hepatitis in a 49-year-old Chinese woman following chronic exposure to dichlorvos. The diagnosis was made two and a half years after initial symptoms of exposure. On initial admission, she was presented with alanine transaminase (ALT) 1558 U/L (Normal: 5–40 U/L), aspartate transaminase (AST) 1267 U/L (normal: 10–40 U/L), total bilirubin (TBIL) 133.5 µmol/L (normal: 3–20 µmol/L), alkaline phosphatase (AKP) 182 U/L (normal: 15–130 U/L). In an animal study, Romero-Navarro and Colleagues (2006) reported that acute exposure to dichlorvos (20 mg/kg/body weight) decreased the activity of hepatic glucokinase in rats. More so, histological changes in liver of rats exposed to dichlorvos has been reported (Owoeye, 2012). There was diffuse vascular degeneration of hepatocytes with necrotic hepatocytes as well as moderate peri-portal cellular infiltration by mononuclear cells in rats exposed for one week. Moderate to severe vacuolar degeneration and necrosis of hepatocytes were reported in rats exposed for two weeks while rats treated for three weeks showed loss of hepatocyte outline. Rats treated for four weeks were reported to have portal triad, completely obscured and circumscribed vessels by connective tissue, necrotic plaque, peri-portal cellular infiltrations and diffuse necrosis.

Renal effect
There is no information on dichlorvos effect on the human renal system. However, an animal study by Hou et al. (2014) examined the nephrotoxicity effect of dichlorvos in rats for ninety (90) days. The study reported significant increase in activities of catalase, glutathione peroxidase and superoxide dismutase; level of malondialdehyde in kidney tissues; serum level of creatinine and urea nitrogen; level of β2-microglobulin, level of retinol conjugated protein, activities of N-acetyl-β-d-glucosaminidase in urine and significant decrease in uric acid level with renal injury including tubular and glomerular filtration. However, an earlier study (NTP, 1989) reported contrasting results of no renal effect on Fisher 344 rats and B6C3F1 mice.

Respiratory effect
Respiratory irritation following dichlorvos exposure was reported in a study (Mathur et al., 2000) involving children. The study reported strong correlation between acute respiratory symptoms and exposure to dichlorvos. However, the authors could not rule out irritant effects of the solvents used to disperse the dichlorvos. An animal study on the acute toxic effect of inhaled dichlorvos vapor on respiratory mechanism in guinea pigs reported significant decrease in respiratory frequency and significantly increased tidal volume in the 35 mg/mL and 75 mg/mL treated animals (Taylor et al., 2008). A histological study on the lungs of rats exposed to dichlorvos reported an extension in the basal associated lymphoid tissue (BALT) in rats exposed for one, four and five weeks (Owoeye, 2012).

Metabolic/endocrine effects
An animal study (Lucic, 2002) on the effect of dichlorvos treatment on butyrylcholinesterase (BuChE) activity and lipid metabolism of rats reported significant decrease in BuChE activity in both sexes of the rats as well as significant increase in triglycerides (60–600%) and total cholesterol (35–75%). In another animal study, rats administered a single dose of dichlorvos equal to 50% of the LD50, were reported to develop hyperglycemia (Teichert-kuliszewksa, 1979). Moreover, cytoplasmic vacuolation of adrenal cortical cells were reported in male Fischer 344 rats following oral administration of 4 or 8 mg/kg/day of dichlorvos for 5 days a week for two years (NTP, 1989).

Dermal and musculoskeletal effect
Vesicle cellulitis and thrombophlebitis of the extremities and bullae appearance have been reported in acute injection of dichlorvos in attempted suicide patients (Cahfer et al., 2004; Sundarka et al., 2000). An earlier report of dermatitis of the neck, anterior chest, dorsal hands and forearms in a 52 year old truck driver who had dermal exposure to dichlorvos was reported by Mathias (1983). In an earlier study (Snow and Watson, 1973), a tenfold increase in serum creatinin phosphokinase, suggestions
of muscle damage (ATSDR, 1997), was reported in greyhound dogs treated with 11 mg/kg dichlorvos capsule. However, contrasting studies (Laudari, et al., 2014; NTP, 1989) reported no gross or histological treatment related damage to skeletal muscles in Fischer 344 rats treated with up to 8 mg/kg/day dichlorvos for 5 days a week for 2 years by oral gavage and B6C3F1 mice treated with up to 40 mg/kg/day dichlorvos for 5 days a week for 2 years.

### Other systemic effects

There was no direct cardiovascular effect on dichlorvos exposure of humans except a generalized study on organophosphate exposure that reported prolonged QT and ventricular extrasystole. However, Durham and Colleagues (Durham, 1957) reported paleness of the extremities, suggestive of poor perfusion in Sherman rats within 2 hours of exposure before death. However, a contrasting report of no gross or histological effects on the cardiovascular system of rats and mice exists (NTP, 1989).

Sclera icterus has been reported following chronic dichlorvos exposure (Zhao et al., 215). An earlier animal study (Ubel, 1987) reported maximal pupillary constriction (pin point pupil) with complete recovery within 4 hours following exposure to household aerosol containing 0.2–2% dichlorvos in rabbit and corneal epithelial erosion and corneal swelling in monkey.

Celic and Colleagues (2009) reported lack of hematological effect except leukocytosis of sublethal dose of dichlorvos in rats following oral administration.

### Diagnostic/biomarkers of dichlorvos exposure

Dichlorvos at high doses will elicit classical symptoms of organophosphate toxicity such as miosis, tremor, increased salivation, lacrimation, pulmonary secretions and perspiration (ATSDR, 1997). Dichlorvos exposure can be diagnosed based on its tendency to inhibit cholinesterase activity. Hence, serum cholinesterase appears to be more sensitive to inhibition by dichlorvos and other organophosphate than erythrocyte acetylcholinesterase. However, serum cholinesterase activity recovers more rapidly than erythrocyte acetylcholinesterase because of the high turnover rate of the serum protein compared to erythrocytes (Kazemi et al., 2012; ATSDR, 1997). In conditions of chronic exposure, the patient may demonstrate only reduced erythrocyte acetylcholinesterase activity and normal serum cholinesterase activity, thus giving false negative result. The true reflection of depressed cholinesterase activity is found in erythrocyte activity. Erythrocyte acetylcholinesterase recovers at the rate of 1% per day in untreated patients and takes about 6 to 12 weeks to normalize, whereas serum cholinesterase levels may recover in 4 to 6 weeks. It is pertinent to note that confirmation (aside patient history) of specific exposure to dichlorvos is difficult as the cholinesterase inhibition is similar to other organophosphate pesticides and requires elaborate analytical chemistry. The rapid metabolism of dichlorvos by liver and blood esterases makes it almost impossible to detect intact dichlorvos in humans and rarely in animals. More so, the major metabolites (dimethyl phosphate and glucuronide conjugate of dichloroethanol) are rapidly excreted into urine and will have left the body within a day or two of cessation of exposure (ATSDR, 1997). Dimethyl phosphate has been measured in the urine of pesticide applicators by extraction with an ion exchange resin, derivitization and gas chromatography (ATSDR, 1997; Das et al., 1983). Dichloroethanol has been detected in the urine of a human volunteer after glucuronidase treatment and gas-liquid chromatography (Hutson and Hoadley, 1972).

### Conclusion

Dichlorvos has become increasingly popular for domestic, industrial and agricultural use, however, the public health concern of dichlorvos has littered toxicological literature indicating possible toxicological implication in unregulated and unrestricted use of the pesticide. The available literature beckons on all the regulatory agencies to live up to their task. Considering the reports of dichlorvos usage and the corresponding biotic and abiotic toxicity, it has necessitated the need to make and enforce stringent rules in the use of dichlorvos containing pesticides. Unregulated and unrestricted use of dichlorvos is a “time bomb” and a matter of public health concern.

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