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Effect of Toxicity Cypermethrin in Animals: A Review

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Despite significant worries about the widespread use of cypermethrin in veterinary, agricultural, and insecticidal applications, there is solid evidence of cypermethrin toxicity for humans. Cypermethrin is a synthetic parathyroid that is catastrophic and for which there is yet no antidote for poisoning. The cypermethrin exposure affects the sodium channel, magnesium, and Apse in the human body. In addition to having neurotoxic effects, cypermethrin also has hepatotoxic effects that cause microtonal enzymes in the liver. Although cypermethrin seems to be more tolerable to animals than to humans, it is nonetheless harmful whether it is ingested or used directly. In this work, we evaluated the existing body of knowledge on the neurotoxicity of cypermethrin and its effects on behavior, molecular level, and reproductive system in humans and animals.

Keywords: Cypermethrin, Toxicity, Mode of Action, half-life, Biochemical and Hematological Effects and Residues

Definition

A synthetic pyrethroid called cypermethrin is administered topically to cattle, sheep, rabbits, dogs, and poultry to control ectoparasites like lice, ticks, and blowflies..(Roberts,1987 ; EMEA,2004) . It can be made into a liquid, semi-liquid, or powder. (WHO, 1989; Sudakin,2006; USEPA,2010).

It is frequently used via dipping, spraying, pouring, and spot-on techniques in veterinary medicine (Harlod et al.,2003; Sudakin,2006). It is sufficiently stable in air and light and has strong insecticidal action with moderate toxicity to birds and mammals. Additionally, it is crucial for protecting plants and using them in agriculture. (Vijveberg and Vanden Braken ,1990;Baker *et al*,2007).

1-2- Pyrethroid classification

One of the synthetic pyrethroids, or compounds made in the same way as the naturally occurring pyrethrin molecule, is cyclomethrin (Harlod et al.,2003; Yilmaz et.al. 2008). Two structurally related subclasses make up the pyrethroid chemical classes. Allethrin, , permethrin, phenothrin, bioallthren, resmethrin, and tetramethrin are examples of ester bond pyrethroids lacking a cyano-group, while fenvalerate, alphacypermethrin, deltamethrin, cyfluthrin, cypermethrin, cyhalothrin, flumeth (JECFA,1997,2000) , cypermethrin have cis and trans isomers (Roberts,1987; Wefco,1989; Sudakin,2006).

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1-3-Chemical and Physical Characteristics

Table (2-1) Chemical Identifications

- Common name	Cypermethrin (CYP.)
- Chemical name	(RS) –alpha-cyano-3-phenoxybenzyl-(1RS,3RS,1RS ,3RS)-3-(2,2-dichlorovinul)-2,2-dimethylcyclopropane carboxylate .
-Chemical Abstracts) Name	(RS)-cyano(3-phenoxyphenyl)methel(1RS)-cis-trans-3(2,2-dichloroethenyl)-2,2-dimethylcyclopropan carboxylate .
-Cypermethrin is a mixture of all eight possible chemical isomers	
Structural formula	C22H19Cl12NO3
Molecular weight	416.3 D
-Chemical structure	CH3 CH3

According to (Roberts,1987 ; Vijverberg and Vanden Braken,1990 ; Atamanalp *et al.*,2002 **).**

Table (1-2) Physical Properties

-Appearance	Yellow –brown viscus liquid to semi-solid crystalline mass
-purity	The commercial preparation 94.2% CYP.
-Melting point	80.5 °C
-Vapor pressure	1.9 X 10 ¯ 7 Pascal at 20 °C
-Solubility g/L at 20 °C Water Cyclohexane Xylen Ethanol Hexane	9.0 X10 – 6 >600 >600 >337 103 >450
-Density	1.23Kg / L at 20 °C
-Octanol water partition coefficient (p)	20 X 10 ¯ 6
-Stability: Hydrostatic Photolytic Thermal Oxidation	Stable under acid or natural conditions but not alkaline conditions . Stable Stable to 220 °C Stable in air at ambient temperatures .
-Avarge of 3pH 's at 20 °C	2.5 X 10 ¯ 7 at m-m 3 /mol

-Soil adsorption coefficient (Koc) (average of data for five soil types)	**6.1X10 $^{-}$ 4 ml /g .**
-Aerobic half -life	**6 X 10 $^{-}$ 20 days**
-Anaerobic half –life	**<14 days**

According to (Roberts,1987 ; Vijverberg and Vanden Braken,1990; Atamanalp *et al.*,2002 **).**

1-4- The History and Uses of Cypermethrin

Chrysanthemum flowers are the source of the natural pyrethrin family, which makes up around 25% of all pyrethrins. (Harlod et al., 2003; Cox, 1996; Tamang et al., 1991) Since the late 1970s, cypermethrin has been utilized extensively around the world for almost 40 years. (Yousef *et al* ,1998 ;C.A.C. ,2003).

About 80% of the pesticides imported into Iraq each year are insecticides.(Heamza,2009). However, the USA alone uses more than a billion pounds of pesticides annually. Pesticides are imported and used in huge amounts in Egypt each year (more than 30,000 metric tons of associated pesticides). (Yousef *et. al.* ,1999). CYP. about 25% of the global market for pesticides.(Khan *et al* ,2009) The majority of CYP produced globally is used to dip or spray insects (such as ticks, lice, and mange) to death. (Harlod *et al.*,,2003). Additionally, it is employed in home remedies and lingers in the air and on surfaces. for around three months, walls and furnishings. It is the fourth most frequent source of pesticide-related sickness among structural pest control professionals in California. (Cox ,1996;Hill *et al.*,2010).

1-5- Mode of Action

The nerve system is CYP's principal target organ. It directly affects the sodium channel, and CYP slows down the sodium channel's closure for many seconds. (JECFA,1997,2000; Seth *et al*. 2000) .

report that prolonged sodium conductance and suppression of potassium conduction reduce peak sodium conductance, which in turn reduces action potentials and recurrent nerve firing, increasing the risk of nerve blockage. The calcium ATPase and the calcium-magnesium ATPase are two examples of the adenosine triphosphate (ATP) that CYP may block in nerve tissue, according to Tucker et al. (1984). Yet another perspective demonstrates that CYP. has an impact on binding to acetylcholine nicotinic receptors.

The CYP functions as a cholinesterase inhibitor in the neurological system, according to Kol et al. (2007). When cholinesterase activity is inhibited, synopses accumulate acetylcholine, stimulating both the central and peripheral neural systems. As a result, the exposure will cause

peripheral muscarinic and nicotinic receptors to interfere with synoptic transmission.

1-6-Pharmacokinetics

1-6-1-Absorption

After oral administration, CYP is quickly absorbed from the gastro-intestinal tract (GIT). (Roberts,1987 ; Tample and Smith,1996 ; Smith *et al*,1996 ; WHO,1996 ; Beyerbach,2000 ; Adriana , 2004) moreover, the gut and pulmonary membranes both have a role in absorption (Reigart, 1999 ; Khanna , 2002 ; Valez *et al*, 2008 Hill *et al*.,2010) . 3.4 mg of soy oil, administered orally in a 50:50 cis: trans ratio. Between 26 and 56% of the given dosage is absorbed by CYP. (Smith *et al* ,1996 ; Tample, and Smith, 1996). The dermal absorption is relatively sluggish since it is difficult to absorb substances via the skin. (Roberts,1987 WHO, 1996 ; Beyerbach,2000 ; Adriana,2004) .

1-6-2-Distribution

Studies on the CYP distribution in many species of mammals have shown that it is swiftly and extensively disseminated to a variety of tissues, namely the lipid and the central and peripheral nerve tissue. (Roberts,1987; Tamang *et.al*.,1991; Khanna,2002).

According to Smith et al. (1996, 1996) & Temple & Smith (1996, 1996), CYP also reached the tissues of the adrenal and ovaries. Within five minutes of intravenous injection in rats, the concentration peaks due to the fast dispersion in the nervous system. (Roberts,1987; Tamang *et.al.*,1991; Iwanika *et al.*,2008) .

1-6-3-Metabolism

Mammals have a quick CYP metabolism (Atamanalp et al,2002).

Ester hydrolysis is the process through which CYP is metabolized in mammals. Conjugation and oxidation (Smith et al,1996 ; Temple and Smith ,1996). As a result of the digestive tract's fast ester linkage hydrolysis, minimal oral toxicity (Beasley,1999) . The central nervous system is hydrolyzed during biotransformation. the ester bond Numerous sites experience oxidation and conjugation also occur. generates a broad range of both primary and secondary water-soluble metabolites that are excreted by the kidneys and bile (Tamang *et.al*.,1991)

CYP and each of its isomers are hydrolyzed to release thebfollowed by oxidation to produce carboxylic acid from the ester link andbDérivés of phenoxybenzoic acid. These byproducts are eliminated asbAlcohols, phenol, and their glycine, sulfate, and glucuronidebor conjugates of glucosides (Roberts,1987; Tamang *et.al*.,1991; WHO,1996; Beasley,1999;EMEA,1998,2003,2004). Animal metabolism with regard to sex or age correlations with the enzyme is not known. (Roberts,1987; Tamang *et.al*.,1991; Beyerbach, 2000) .

1-6-4-Excretion

oral dose of CYP 3.8 mg/kg demonstrates quick results. Approximately 61% of this dosage was eliminated after 50 hours (43% by urine and 22.5% feces). (Roberts1987; WHO,1996; Beyerbach,2000 ; Adriana *et al*,2004).

When CYP is administered topically to sheep at a dosage of 2.7%, it disappears after 6 days through urine and feces. In two days following oral delivery, around 65% is removed.(Tamang *et.al*.,1991;Carne *et al* 2007). Rats are given an oral dosage of CYP4 mg/kg as Soya oil basis. maximal excretion rates between 5 and 10 hours after administration. (Tample and Smith ,1996).

Two groups of milking cows are given different doses of CYP twice daily—0.3 mg and 12 mg per kilogram of feed—in cows. The findings demonstrate that the principal routes of excretion are through urine and feces and that milk only contains a small portion of the dosage. (Roberts1987;Woolen *et.al*.,1992) .

Additional research was done on rats, hens, sheep, and comparable findings from the cows, with the exception of the milk, where less than 1% is expelled.(Tamang *et.al*.,1991 ; Carne *et al*, 2007).

The topical application of CYP typically results in a slow elimination. For instance, when CYP was applied topically at a dose of 22 mg/kg to sheep, less than 0.5% of the dose was excreted at 42 hours, and only 2% was removed from the body after 6 days later via the urine, while 0.5% was excreted at 6 days later through the feces. Nevertheless, about 35% of treated sheep were found to be healthy. (Roberts1987; WHO,1996; Beyerbach,2000 ; Khanna,2002; Adriana,2004) .

1-7-Toxication

1-7-1-Lethal Dose (LD50)

In each animal species administered with CYP in the tests, there is no stable or conventional LD 50. Each animal species' LD50 varies according to:ratio of cis to trans isomers and The formulation-related vehicles. (He *et al*.,1989; Dorman and Beasley,1991; Cox,1996;Tample and Smith, 1996; Jagvinder *et al*. ,2001).

Toxic reactions, however, are discovered to be consistent across all species. (Tample and Smith,1996; Venkateshwaralu *et al*.,1997; Jagvinder *et al*. ,2001). For the following reasons, searchers and investigators hold varying opinions on what constitutes a fatal dose: According to Smith et al. (1996), mice have an oral LD50 of 80-769 mg/kg bw whereas rats have a range of 190-325 mg/kg bw for males and 160-520 mg/kg b.w for females. In rats, the dermal exposure LD50 is 1630 mg/kg b.w., however in rabbits, it is greater than 2100 mg/kg.

According to Ecobichan (1991), the oral LD50 for rats varies from 250 to 2500 mg/kg BW, whereas for mice it is 380 mg/kg BW. According to EMEA (1998, 2003, 2004), experimental tests of CYP in maize oil in the cis-trans ratio 85: 15 reveal that the LD50 is 380 mg/kg in female rats and 890 mg/kg in the cis-trans isomer ratio of 35: 65. According to Crane et al. (2007), the oral LD50 in rats and mice is about equivalent to 85 to 3995 mg/kg. According to EPA (1998), the LD50 in rats is as follows:

-260 mg/kg b.w. taken orally

-Dermally, 2400 mg/kg body weight
-The LC50 for inhalation is 3 mg/liter (L).

Tample and Smith (1996) show that For animals, the oral hazardous dosage is larger than 150-1100 mg/kg. It was greater above trans isomers >3000 mg/kg in rats, ranging from 150 to 350 mg/kg in cis(Tample and Smith (1996).

The LD50 in rats is 250(197-336) mg/kg for males and 300 (100-450) mg/kg for females, according to PMEP (1989), whereas in rabbits, the dermal LD50 is >2500 mg/kg and the main dermal irritation is 0.81. For pharmacological effects, the subchronic oral dosage in rats is 73 ppm (No Observed Effects Level, or NOEL). The NOEL for harmful effects is 160 ppm. Low Observed Effects Level (LOEL) was 510 ppm while the NOEL for chronic toxicity in rats was 160 ppm.

1-7-2- Cypermethrin Toxicity

CYP is deemed to be hazardous at a class II level. On the product label of pesticides containing CYP, the signal words CAUTION or WARNING are present. (He *et al*.,1989,Ecobichan,1991;WHO,1997; Reigart,1999) . Age, animal species, environment, the ratio of cis to trans isomers, and the types of vehicles utilized are only a few of the variables that affect toxicity. (Venkateshwaralu *et al*.,1997; EMEA, 1998, 2003 ,2004 Amelotti *et al*.,2009) . The wildlife toxicity of synthetic pyrethroids is 1000 times greater than that of their precursor compounds (VMD, 2010). Due to GIT's hydrolysis of the ester bond after oral delivery, the toxicity decreased. (Beasley,1999) .

1-7-2-1- Acute Toxicity

In the event of cutaneous absorption or ingestion, CYP is moderately hazardous.(Wefco,1989;Temple and Smith,1996;WHO,1996;FMC,2003). After oral ingestion, the symptoms of poisoning manifest within a few hours, and survivors recover within three days. (Tample and Smith,1996 ;WHO,1996; -Yilmaz *et al*.,2004) . Ataxia, gait irregularities, tip-toe walking, salivation, lacrimation, tremors, colonic convulsions, numbness, tingling, itching, burning feeling, loss of bladder control, incoordination, seizures, and perhaps death are among the dermatologically documented indications of a high dosage. (Smith *etal.*,1996;Shah *et al*,2007). There are negative consequences of CYP on the brain (Hayes and Laws,1990 ; Chapman *et al*,1993 ; IPCS,1995; Tample and Smith,1996 ; WHO,1996 ; Reigarts,1999 ;FMC,2003 ; Crane *et al*,2007 ; Kol *et al*.,2007). Animals that survive become well in seven days.(Smith *et al.*,1996; Sarkar *et.al*.,2005;WHO,1996).

Regarding the respiratory consequences, several clinical symptoms have been noted, including coughing, pulmonary edema, and shortness of breath (Tample and Smith, 1996). Following dermal contact, CYP causes temporary tingling and itchy skin sensory responses.(Tample and Smith,1996;Shafer *et.al*.,2005). Dermatological side-effects have been documented by (Smith et al., 1996; Temple and Smith., 1996; O'Malley, 1997) and include temporary congestion, red papules, and edema of the skin. Constant nausea, persistent vomiting, stomach pain, and diarrhea, which later develop into convulsions, unconsciousness, and coma, are symptoms of

high-dose consumption. (Wefco,1989 ; Hayes and Laws,1990 ;Reigarts,1999 ; Tample and Smith,1996 ; FMC,2003; Yilmaz *et al*.,2004 ;Kol *et al*.,2007 and Wikipedia, 2010) . along with mortality, tremors, paralysis, respiratory failure, and hypersalivation. While (Temple and Smith, 1996) observed skeletal and smooth muscle effects, including muscular fasciculation in limbs. There have been reports of the gastrointestinal tract, including epigastric discomfort, anorexia, nausea, and vomiting (Smith,1996; Tample and Smith,1996) Headaches, Sneezing, nasal stiffness, lack of coordination, tremors, nausea, face edema, and convulsions are examples of inhalation symptoms. (Reigarts,1999).

High doses of CYP may cause hyperesthesia, clenching of the teeth, trembling of the muscles, excessive salivation, dyspnea, uncoordinated behavior, opisthonos, and even death in sheep. (Khan et al 2009).

Head shaking, listlessness, weariness, convulsions, moderate consciousness abnormalities, and coma may be experienced as effects on the (CNS) and system (PNS) (Tample and Smith,1996).

1-7-2-2-Subchronic Toxicity

According to Ecobichan (1991), CYP has a low longterm toxicity for humans. Animal symptoms include moderate anemia, slowed growth, increased liver weight in rats, decreased weight gain, and increased liver weight in mice. Inability to move with coordination, lack of appetite, and tremors are the symptoms in dogs, whereas CYP causes pathological alterations in the liver, skin, adrenal glands, lungs, and thymus in rabbits.(EPA,1998).

1-7-2-3- Chronic Toxicity

According to Ecobichan (1991), CYP has a low longterm toxicity for humans. Animal symptoms include moderate anemia, slowed growth, increased liver weight in rats, decreased weight gain, and increased liver weight in mice. Inability to move with coordination, lack of appetite, and tremors are the symptoms in dogs, whereas CYP causes pathological alterations in the liver, skin, adrenal glands, lungs, and thymus in rabbits. (Ray,2007; FMC,2003).

Itching, prickling, and localized burning sensations on the skin linger for around three days. (Ecobichan,1991, Chauhan,2006 eHow,2007)

1-7-2-3- Aggregate Exposure

The tolerance for dietary exposure (food) to CYP residues in horses, goats, cattle, and sheep has been documented.(EPA,1998; Ray,2007).

1-7-3- Safety

At the highest doses of 60 mg/kg/day for rats and 600 mg/kg/day for rabbits, there was no sign of developmental toxicity in either the rats or the rabbits. In each research, there was no fatality, although there was a fall in body weight.(EPA,1998).

1-8- Cypermethrin Effects

This inquiry demonstrates the withdrawal period, half-life, systemic, enzyme alterations, hematological, and histological impacts of CYP on animals and the environment.

1-8-1- Period of Withdrawal

Depending on the animal species and CYP concentration, there are differences between these times as follows:

Table (1-3) lists the withdrawal times for cattle and sheep.

Cypermethrin concentration	Animal	Meat
1.20 % w/v	Sheep	6 days
1.4 % w / v	Sheep 10 ml/10kg / b.w.	6 days
3 % w / v	Cattle 10 mg / animal	8 days
7 % w / v	Sheep	15 days
8 % w / v	Cattle	Slow

According to (Mehhorn *et al*.,2007 **)**

1-8-2- Cypermethrin half – life

1-8-2-1- Cypermethrin Biological half – life

According to WHO,(1996), the excretion half- life in rats is one week and in mice is 20 to 30 days, although IPCS,(1995) claimed that in humans, the excretion of metabolites CYP was complete in two days after the last treatment of 1.5 mg/kg/day. However, this is different in rats, where studies have revealed that over 99% was expelled within hours, and the remaining 1% is retained in the body fat. The cis isomer's eliminated half-life, however, is 18 days.

Following oral administration of CYP to volunteers, the biological (by route of exposure) elimination half-life was 15.5 5 hours (range 12-26 hours), whereas the cutaneous exposure had a shorter half-life of around 13 5 hours (range 10 – 22 hours).

1-8-2-2- water and Soil half –life

Between researchers and investigators, it differs. According to some of them, the CYP degrades quickly but not continuously (WHO, 1997).

Other experts and investigators stated that the Environmental Quality Standard (EQS) and Drinking Water standard are exceeded by the compound, with the half-life of the compound in soil ranging from 8 to 14 days (DW) (Jin andG.R.B.,1998; PAN,2000). Dalali et al. (2002) claim that the CYP undergoes hydrolysis in the soil after 16 weeks and that the half-life is 5 days; however, SEPA and VMD (2006) demonstrate that the CYP continues to be biologically active in the soil after 133 days. It is photo stable and has an 8–16 day half-life in direct sunshine. The half-life is 56 and 100 days, respectively, in the soil and water (Shah et al., 2007).

CYP is stable in naturally occurring acidic environments (pH 3–7), although its hydrolysis in strongly alkaline solutions (pH 12.5–13.5) degrades over 225 °C. (Ostize and Khan,1994 ; Dalali *et al.*,2002;Crane *et al*., 2007).

Field data indicate that (in practice) it is stable in air and light.The biological hydrolysis half – life is 62 weeks at pH =7.5. The rate of degradation depend upon soil type so the half – life in the sandy soil is 3- 4 weeks (Chapman *et al.*,1993 ; FAO,1996;Crane *et al.*,2007). In the rich soil, the half-life ranges from three to five weeks. It declines where the median half-life is two weeks in natural water (Tample and Smith,1996).

Reigart (1999) demonstrated that CYP had a half-life of 9 to 18 days in direct sunlight, indicating that it was quite stable. Studies have revealed that the half-life in soil might last up to 120 days. CYPpersists for around three months when receiving home therapy.(Reigart, 1999).

1-8-3- Toxic Effects of Cypermethrin

1-8-3-1- Biochemical and Hematological Effects

Plasma total lipids, triglyceride, cholesterol, very low density lipoprotein (VLDL), low density lipoprotein (LDL), glucose, creatinine, urea, and total bilirubin significantly increase in rabbits given a sublethal dose of CYP (125 mg/kg bw), whereas high density lipoprotein (HDL), total protein, albumin, globulin, and A/G ratios do not change significantly. (Yousef, *et al.*,1998 ;Khan *et al*.2003; Yousef *et al*.2003) .

Total Red blood count, Hb%, and PCV are all decreasing in blood, but Total White blood count is increasing. (Yousef *et al*.2003) According to studies on sheep, CYP treatment in goats resulted in an increase in MCV with substantial reductions in Hb, red blood count, MCHC and PCV (Tample and Smith,1996 ;Yousef, *et al*.,1998; Samita *et al*.,1999; Khan,2005; aAhmad *et al*.,2009;Khan *et al*.,2009) .

Significant reductions in ALT, ALP, and AST are also observed in sheep treated with CYP. (Yousef, *et al*.,1998) , however in lambs given CYP, ER cholinesterase concentrations and blood cholinesterase were suppressed. (Yousef, *et al*.,1998 ; Khan *et al*.,2003). Hb%, PCV and red blood count in mice, however, are reported to have increased significantly by Ahmad et al. (2009). With CYP treatment, anemia may or may not be produced in rabbits.

1-8-3-2- Immunological effects

Following injection of CYP, rabbits develop a humoral immune system response against S. typhi. Reduced cell-mediated immunological response (Desi *et al*.1986; EMEA, 1998, 2003,2004; Liu*et al*.,2006). Additionally, CYP affects the tuberculin skin test.(Cox, 1996). .

1-8-3-3-Reproductive Effects

In terms of teratogenic consequences, CYP can have an impact on the number of organs and skeletal deformities in the offspring in pregnant rabbits, while delaying processes like tooth emerging and eye opening in rats and increasing the production of defective sperm in mice.(Chapman et al., 1993; He et al., 1989)

The effects of CYP on semen features and concentrations are examined in one study involving 35 male dwarf goats. A decrease in ejaculatory volume, motility percentage, mass activity, alkaline PH, color shift from creamy to milky-straw, and a rise in the proportion of defective

spermatozoa and mortality are among the impacts that were discovered. **(**Ahmad *etal*.2009

1-9- Residues of Cypermethrin in Ruminant Tissues

Bovine, ovine, and caprine species of ruminants have a similar pattern. intestine and gastro-physiology. The pharmacokinetic data and Data on residue depletion do not show any appreciable variation. hence, it is assumed that additional animals exist between sheep, cattle, and goats. Ruminants are unlikely to exhibit any discernible variations in these the settings. (EMEA,1998,2003,2004).

Bovine and ovine species' current tissue maximum residue limits (MRLs) are the same, hence it is deemed suitable to advocate extending the MRLs so that all ruminants would have access to the same tissue MRL values. It is also advised that the MRL for milk from cows be applied to all ruminants. (EMEA,1998,2003,2004)

However, searchers claim that there are several different MRLs, as seen below: According to some researchers, the MRLs for cattle and sheep are 55 g/kg for whole milk and 230 g/kg in the fat, muscles, liver, and kidney. (Beyerbach,2000 ; FAO/WHO,2002) .

(EMEA,1998,2003,2004) noted the following MRLs in ovine and bovine tissues: 20 g/kg of muscle, 200 g/kg of fat, and 20 g/kg of muscle were identified in the liver and kidney. 20 g/kg of bovine milk residues were found .

1-9-1- Residues in Sheep

After receiving oral doses of 1 mg/kg b.w. of CYP in three groups of six adult sheep of both sexes, the animals were slaughtered one, two, and four days later. It was discovered that the main values of total residues were three times higher in the liver than the kidney and roughly 1.3 times higher than in the fat at six days. (Beyerbach,2000 ; FAO/WHO, 2002). However, in another trial, 4 sheep were given an oral dosage of 1.5 mg/kg b.w., and after 8 days of therapy, the sheep were killed. The percentages of residues in the kidney, liver, fat, and muscle, respectively, are 4.2, 22, and 85% of the total residue. (Smith *et.al*,1996 ; EMEA,1998,2003,2004).

1-9-2 - Residues in Goats

In a different trial, goats were given a topical application of a commercial pour-on formulation containing 5 mg of CYP per kg of body weight. The mean residues in kidney fat were 6 g/kg at day 6, 150 g/kg at day 15, and 12 g/kg at day 40 after treatment, according to the residues at the following points. In a different trial, nursing goats were administered with the same amount of pour-on (5 mg/kg b.w.), and the residues in the milk were 22 g/kg after one day, 20 g/kg at 30 hours, and less than 15 g/kg at four days. (EMEA, 1998,2003 ,2004).

1-9-2- Residues in Cattle

Milk residues from animals fed a diet containing 12 mg/kg of CYP showed 92% of both cis and trans isomers. 98% of fat eliminated using a solvent extraction. Furthermore, 93% of the fat residue has been shown to be the parent CYP. In kidney, it is present in muscle at 11 g/kg. (Roberts,1987) .

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Another study demonstrates that oral-dosed calves that are butchered on the last day of dosing still had cyp residues:

Table (2-6): Cow CYP Residues in Oral Dose.

Dose mg / kg feed	Milk	Kidney	Muscle	Liver	Renal fat	Subcutaneous fat
0.3	1.3	3.4	< 1	4.7	10.12	8.9
5.5	13.5	50 – 130	< 45	110	30 -100	10 -60
10	32	110	10	200	100	80

According to (Beyerbach,2000)

These values were measured by µg / kg except for milk which is measured by µg / l (Beyerbach,2000).

In lactating cows administred twice daily with CYP in the doses 0.2 , 5 and 10 mg per kg of food , the residues in tissues measured after 7, 20 , and 21 days of treatment are low and in the following order : liver >kidney > renal fat > subcutaneous fat > blood > muscles > brain . Then residues are measure in the liver and kidney of cows that received 10 mg / kg of diet . (Woolen *et.al.*,1992; Chen *et.al.*,1997).

Calves are treated topically with a pour – on formulation at approximately 41 mg / kg b.w and then killed in groups of 5 animals at 3 , 7 , 14 days after treatment . the liver residue is 10 µg / kg in all groups , while in the muscles it is detected only in the day 3 .Samples mean residue is 24 µg / kg , while in kidney the residues are 66 µg / kg at the 7^{th} day and 40 µg / kg at the 14th days of treatment . Residues are the highest in fat :the mean residues are 260 µg / kg and 670 µg / kg and they are found in the subcutaneous and perirenal fat respectively at the 7th days after treatment . while, at 14th days, they are 140 and 330 µg / kg . (Chen *et.al.*,1997;EMEA,1998,2003,2004).

In lactating cows treated topically with pour – on CYP at a dose of 1.25 mg / kg b w residues are 25 µg / kg in the milk at 24 hours after treatment ,48 µg / kg at 48 hours after treatment and 7 µg / kg at 7 days after treatment . (Chen *et al.*,1997;EMEA,1998,2003,2004)

When cows are treated topically with 2.5 mg / kg bw of cyp. the mean residues in milk at the 3 time – points are 63 µg / kg , 99 µg / kg and 13 µg / kg respectively (Chen *et.al.*,1997;EMEA,1998,2003,2004).

2-10- Treatment and Management

There is no antidote for humans (Flannigan et al. 1985), however treatment involves avoiding the ingestion of milk, cream, or other items that include animal or vegetable fat since they increase absorption. Sedation, such as with barbiturates, is necessary to regulate CNS stimulation. Ordinary salves have been proven to be helpful in easing discomfort when a reversible skin feeling (paresthesia) occurs.(FMC,2003). But keep in mind that the goal of therapy is primarily to relieve symptoms and stop additional absorption. 1985 (Flannigan et al.). Convulsions are managed by the proper treatment regimen when bronchospasm or

anaphylaxis strike.Eye pollution is treated for a long period with plenty of water or saline..(Flannigan *et al.*1985 ; Chapman *et al*.,1993 **).**

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