STATE OF MICHIGAN

Health Consultation

Technical Support Document for DDT, DDD, and DDE Reference Dose (RfD) as the Basis for Michigan Fish Consumption Screening Values (FCSVs)

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Summary

Dichlorodiphenyltrichloroethane (DDT) and its metabolites continue to be detected in the filets of a variety of fish species in Michigan surface waters, particularly those caught from the Great Lakes. Beginning in the 1970s, the Michigan Department of Community Health (MDCH) has provided guidance on the safe consumption of fish contaminated with these chemicals.

MDCH reviewed summaries of the toxicology and epidemiology of DDT and dichlorodiphenyldichloroethylene (DDE) (ATSDR, 2002; WHO, 2010) and conducted searches of the currently available scientific literature to identify the primary adverse health effects associated with these chemicals.

MDCH selected a chronic reference dose (RfD) of 1.6×10^{-4} milligrams per kilogram of body weight-day (mg/kg-day) for DDT and its metabolites for use in the Michigan Fish Consumption Advisory Program (MFCAP). This RfD was based on the US Environmental Protection Agency (EPA) RfD for DDT with an adjustment for an incomplete database related to mutagenicity.

Purpose and Health Issues

Some fish species from certain Michigan waters are contaminated with DDT and its metabolites. Michigan has issued fish consumption advisories regarding DDT for over three decades. The purpose of this document is to review the available literature on DDT and its metabolites and recommend changes in the MFCAP, if necessary, to ensure that the consumption advice remains protective of public health.

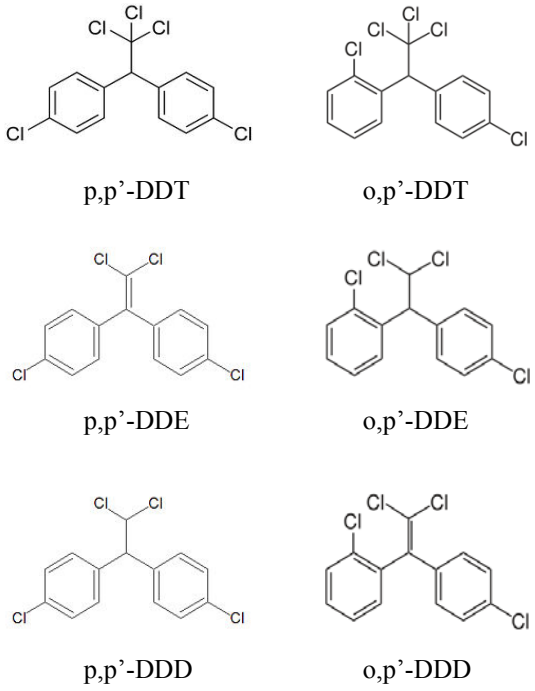

Figure 1. Chemical structures of DDT and its metabolites.

Background

Prior to 1972, DDT, a human-made chemical, was used widely in the United States (US) as a broad spectrum insecticide (ATSDR, 2002). DDT is not a naturally occurring chemical. US production was 56 million kilograms (kg) in 1960 and peaked at 82 million kg in 1962 before declining to 2 million kg in 1971. US production of DDT continued until at least 1985 when US exports were 303,000 kg (ATSDR, 2002).

Once DDT enters the environment, it can undergo chemical transformations though abiotic and biotic processes. Photooxidation, an abiotic process, has been shown to degrade DDT to DDE. Metabolism by bacteria, a biotic process, can create

multiple transformation products, including DDE and dichlorodiphenyldichloroethane (DDD). Thus, DDT, DDE, and to a lesser extent DDD are commonly found together in sediment or biota. When DDT enters people, it will first be metabolized to DDE and DDD, followed by other transformation products before finally being released from the body, primarily in urine. DDE and DDT have the longest half-lives and will stay in the body for the longest amount of time. A total of six DDT, DDE, and DDD chemical structures can occur (Figure 1), however, not all forms are found equally in the environment (ATSDR, 2002).

DDT and its metabolites released to surface water are persistent in sediment. These chemicals are highly lipophilic, can accumulate in biota, and biomagnify up the food chain (ATSDR, 2002). When fish are present in a waterbody, they define the upper part of the aquatic food web. Fish species that live longer, have higher lipid content, and eat other fish accumulate the greatest amount of DDT. Elevated concentrations of DDT or its metabolites in fish filets have raised questions about human exposure and the risk of negative health effects. MDCH has issued fish consumption advisories due to DDT and its metabolites since at least 1977 (Michigan Fishing Guide 1977).

The purpose of this document is to review the available literature on DDT and its metabolites and recommend changes in the MFCAP, if necessary, to ensure that MDCH fish consumption advice remains protective of public health. The primary literature sources for this document are: (1) the World Health Organization (WHO) Environmental Health Criteria 241 (WHO, 2010), which provides a comprehensive review of DDT and DDE literature up to 2010; (2) the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicology Profile for DDT, DDE, and DDD (2002), and the EPA Integrated Risk Information System DDT and DDE summaries (EPA, 1996).

Discussion

Environmental Contamination

Filets from fish harvested in some Michigan waters have been found to contain DDT and its metabolites (DEQ, 2011). DDT and associated metabolites are quantified as a summed total of the concentration of six chemicals (Figure 1) commonly analyzed for by the Department of Environmental Quality (DEQ) Fish Contaminant Monitoring Program (FCMP) (DEQ, 2011). The most prevalent of these in Michigan fish filets is p,p'-DDE, which typically exceeds eighty percent of the summed concentration of DDT and its metabolites (personal communication with Joe Bohr, DEQ). Detected concentrations of the sum of DDT and metabolites in the most recent fish filet analyses from 20 locations in Michigan ranged from below the analytical detection limit (0.001 parts per million (ppm)) to 2.98 ppm.

Some Michigan waters have known DDT contamination due to a release from a point source, such as the Velsicol Chemical Corporation on the Pine River in Gratiot County, Michigan. DDT was produced at the Velsicol plant, which closed in 1978. The site was designated an EPA

Superfund Site in 1983. The fish in the Pine River continue to have some of the highest DDT concentrations found in Michigan fish and anglers are advised to not eat any fish from that segment of the Pine River.

In addition to point source releases, DDT and its metabolites can also be found in fish from Michigan surface waters as a result of atmospheric deposition. Semi-volatile chemicals such as DDT can undergo long-range transport through a process of "global distillation" (ATSDR, 2002) in which DDT repeatedly volatilizes and is transported via the atmosphere to new location where it is deposited. Larger and colder waters will retain DDT for longer periods of time allowing greater probability that bioaccumulation and biomagnification will occur. In Michigan, fish living in the Great Lakes or large lakes near the Great Lakes are contaminated with DDT. Furthermore, river segments connecting to the Great Lakes often have fish contaminated with DDT.

Exposure Pathway

An exposure pathway contains five elements: (1) the contaminant source, (2) contamination of environmental media, (3) an exposure point, (4) a human exposure route, and (5) potentially exposed populations. An exposure pathway is complete if there is a high probability or evidence that all five elements are present. Table 1 describes human exposure to DDT and its metabolites.

Table 1. Human exposure pathways for DDT contaminated fish filets.

Source	**Environmental Medium**	**Exposure Point**	**Exposure Route**	**Exposed Population**	**Time Frame**	**Exposure**
Atmospheric deposition, non-point source runoff, or point-source release of DDT into Michigan Waters	Fish (accumulation through the food chain)	Fish filets	Ingestion	Anyone who eats these fish (residents and tourists)	Past, Present, and Future	Complete

Toxicological Evaluation

Toxicokinetics

Approximately 70-90% of the administered oral dose was absorbed by rats fed DDT in vegetable oil (ATSDR, 2002). The intestinal lymphatic system is the primary entry into the body with direct entry into blood being a secondary pathway (ATSDR, 2002).

There is more than one pathway in mammals for the metabolism of DDT. Rodents and humans have similar metabolic pathways for DDT with both initially metabolizing DDT in the liver to DDE and DDD. DDE and DDD are further metabolized through a series of steps involving reduction, hydroxylation, and oxidation that removes chlorine atoms from the aliphatic portion of the molecule. The major metabolic pathway ends with 2,2-bis(p-chlorophenyl) acetic acid (DDA), which is excreted in urine (ATSDR, 2002).

The half-life of DDT and DDE varies between species of mammals. In humans, DDT has a half-life of around 5 years and DDE of 13-15 years (WHO, 2010). Elimination from the body of o,p'-DDT may be dose dependent, such that lower doses result in longer half-lives and higher doses shorter half-lives (WHO, 2010). Consumption of DDT contaminated fish will result in these chemicals entering the body and partitioning into fat. Given that five half-lives are required for greater than ninety-five percent of DDT to be eliminated from the body, some amount of DDT will remain in a person's body for at least two or three decades after exposure.

Hazard Characterization

The WHO conducted a comprehensive review of published DDT and DDE toxicology and epidemiology literature that included studies published through 2010 (WHO, 2010). DDT is metabolized to DDE in mammals including humans; therefore people who eat contaminated fish will be exposed to DDT as well its metabolites.

A basic difference between toxicology and epidemiology is that toxicology tests chemicals on animals in a controlled and known manner (i.e., experimental), whereas epidemiology observes human outcomes in situations where people were unintentionally exposed to the chemical. Using animal studies and experimental methods, causal relationship between the chemical exposure and the negative effect can be assessed. The observational epidemiology studies can only assess associations between the chemical exposure and a change in human health. Results from epidemiology studies may be caused by multiple factors including other chemical exposures, current health status, lifestyle choices, or genetics. Use of both animal and human studies provides the best available evaluation of the health risks people may encounter when eating fish contaminated with DDT and its metabolites.

Cancer

The EPA has determined that DDT, DDD and DDE are probable human carcinogens based on the observation of tumors in multiple experimental studies using mice or rats (EPA 1988, EPA 1996). Three observational epidemiology studies have been published in the last 10 years that identify statistically significant correlations between DDT or DDE and liver, testicular or breast cancer (WHO, 2010). A study of US servicemen found serum DDE concentrations greater than 0.39 micrograms per gram lipid (μg/g) were correlated with the development of testicular cancer

(RR=1.71; 95% CI=1.23-2.38) (McGlynn et al., 2008). Exposure of Chinese residences of Linxian, China to DDT was correlated with liver cancer (odds ratio (OR) for quintile 1 vs 5: 3.8; 95% confidence interval (CI) = 1.7-8.6) (McGlynn et al., 2006). The *Child Health and Development* study, a longitudinal cohort study in California, found that prepubertal exposure to p,p'-DDT was correlated with increased incidence of breast cancer. Women, exposed before the age of 14 years old, in the second exposure tertile (8.1-13.9 µg/L) had an OR of 2.8 (95% CI = 1.1-6.8) and those in the third tertile (>13.9 µg/L) had an OR of 5.4 (95% CI = 1.7-17.1) (Cohn et al, 2007). This increase across tertiles was a significant ($p<0.01$) linear trend (Cohn et al, 2007). WHO concluded that the McGlynn studies (2006, 2008) were strong evidence of association between DDT, DDE and liver, testicular cancer, respectively (WHO, 2010). The preponderance of breast cancer studies suggest that adult exposure to DDT or DDE do not support an association, however, prepubertal exposure to DDT may pose a risk (WHO, 2010). A study of workers who applied DDT to combat the spread of malaria during the 1940s did not find an association between DDT exposure and liver cancer, pancreatic cancer or leukemia. (Cocco et al., 2005). Inadequate data exists to assess the association between DDT or DDE and lung, pancreatic, prostate or endometrial cancers (WHO, 2010).

The carcinogenic mode of action (MOA) for DDT and its metabolites is unknown, however, it is expected that more than one MOA may be involved. Early reviews of the genotoxicity of DDT concluded that it was not genotoxic to rodent or human cell systems and was not mutagenic to bacteria (EPA, 1996; ATSDR 2002). A more recent review concluded that DDT was inactive in most genetic toxicity assays, however recent publications report deoxyribonucleic acid (DNA) damage in human lymphocytes studied both *in vitro* and in biomonitoring studies (WHO, 2010). DNA damage has been found in peripheral blood mononuclear cells (PBMC) collected from adults and children exposed to DDT and DDE (Perez-Maldonado et al., 2011; Perez-Maldonado et al., 2006; Perez-Maldonado et al., 2005). Children with greater exposure to DDT and DDE also had the greatest amount of measured DNA damage (Perez-Maldonado et al., 2011). *In vitro* assays exposing human lymphocytes to DDT or DDE have been shown to cause DNA damage (Gajski et al., 2007; Ennaceur et al., 2008). The mechanism by which this DNA damage occurs is not known, however, *in vitro* assays with human PBMCs found exposure to DDT and DDE can increase the level of reactive oxygen species (ROS) (Perez-Maldonado et al., 2005). However, another *in vitro* study of human lymphocytes that found DNA damage did not detect oxidative stress (Geric et al., 2012). Rat lymphocytes, exposed to DDE, had increased lipid peroxidation and DNA damage (Canales-Aguirre et al., 2011).

DDT is a cancer promoter in two-stage initiation-promotion liver experiments using rats (WHO, 2010; ATSDR, 2002). DDT can affect hormone receptors, inhibit intercellular communication, and alter DNA methylation (WHO, 2010).

Non-Cancer

Low-level DDT and DDE exposure is associated with hepatic, reproductive, developmental and endocrine effects. Other endpoints have been reviewed and discussed by other agencies (ATSDR, 2002; WHO, 2010) and are not covered in this overview.

Liver: In animals, the liver appears to be a sensitive target for DDT (ATSDR, 2002). In rats, doses greater than or equal to 5 mg/kg-day caused liver enlargement, increased liver enzymes, liver cell enlargement, and necrosis (WHO, 2010; ATSDR, 2002). Studies of workers that either manufactured or applied DDT were not able to detect liver damage using blood tests for liver enzymes, however some associations with increased gamma-glutamyl transferase (GGT) were reported (WHO, 2010), which can be an early sign of liver damage. A residential study of 499 individuals living near a closed DDT plant found elevated DDT and DDE serum levels in the residents and a positive association existed between these chemicals and gamma-glutamyl transferase (GGT), serum cholesterol, and triglycerides (Kreiss et al., 1981). However, serum cholesterol and triglycerides were not reported as being abnormally elevated, nor was obesity found to be correlated with DDT (Kreiss et al., 1981).

Reproductive: Multigenerational animal studies of DDT have not found impairments of fertility, fecundity, or pregnancy. Animal studies in rats have reported consistent results demonstrating that DDT and DDE exposure affects male hormones and sperm formation resulting in altered sperm counts and motility (WHO, 2010). DDE is anti-androgenic and o,p'-DDT is weakly estrogenic *in vitro*. Animal studies have documented that high exposures result in reduced anogenital distance, nipple retention, hypospadias, and cryptorchidism (WHO, 2010).

Multiple human studies have observed associations between DDT and DDE exposure and adverse effects on semen parameters such as sperm count, motility and morphology (WHO, 2010). DDE exposure was associated with increased percentage of sperm cells with two sex-chromosomes, instead of the appropriate single sex-chromosome (McAuliffe et al., 2012). Women (219 participants) with the highest serum p,p'-DDE levels (>23.6 parts per billion (ppb); 5^{th} quintile) reached menopause 1.7 years earlier than women with the lowest levels (<5.5 ppb ; 1^{st} lowest quintile) (Akkina et al., 2004). Participants in several of these studies had exposure to other chlorinated organics in addition to DDT and DDE, which may have confounded the study results. The observational epidemiologic studies are inadequate to assess DDT or DDE effects on male or female fertility and fecundity.

Developmental: DDT and DDE have been associated with negative effects on human fetal development. Two observational studies found an association between DDT or DDE levels and fetal loss. One study of 1,717 women, reported an adjusted odds ratio for fetal loss of 1.4 (95% confidence interval 1.1-1.6) for each 60 micrograms per liter (µg/L) increase in DDE blood serum levels (Longnecker et al., 2005). However, the authors indicated that this finding was inconclusive due to the potential that measured DDE serum levels may not accurately reflect the

mother's true exposure to DDE. Some participants had carried children to term, while others had only experienced fetal loss. Many factors can cause fetal loss unrelated to DDE exposure, yet the length of a pregnancy can affect DDE serum levels. The authors noted the possibility that previous pregnancies ending in fetal loss may have decreased serum DDE levels less than pregnancies carried to term. Women who carried more children to term would have lower DDE levels than those which only experienced fetal loss, thus altering participants' DDE levels and making them less representative of participants' true DDE exposure. This potential bias in serum DDE levels could not be accounted for, thus making their finding inconclusive. The second study was of Chinese female textile workers who experienced spontaneous abortions. Of the 42 cases, 15 were randomly selected and matched to 15 controls. After adjustment for age and body mass index, each one nanogram of p,p'-DDE per gram of serum (ng/g) increase was associated with a 1.13 (CI, 1.02-1.26) increased odds of a spontaneous abortion (Korrick et al., 2001).

The WHO review concluded that the available evidence at the time of their report did not suggest an association between DDT or DDE and restrictions on fetal growth (WHO, 2010). However, a more recent study of 350 boys between the ages of eight and nine years old found that exposure to a mixture of organochlorines including DDE, was associated with significantly lower mean body mass index and significantly lower mean height (Burns et al., 2012). Epidemiology studies provide mixed but supportive evidence for an association between early life exposures to DDE and reduced childhood or pubertal growth (WHO, 2010). A prospective study of prenatal exposure to DDE, DDT, and PCBs reported non-dose response associations between DDE and being overweight (Valvi et al., 2012). Differences existed between boys and girls. The increased risk of being overweight was significantly higher in the third tertile of PCB exposure [RR = 1.70; 95% confidence interval (CI): 1.09, 2.64] and the second tertile of DDE exposure (RR = 1.67; 95% CI: 1.10, 2.55), but no association with DDT exposure was found in the overall population.

Consistent neurocognitive effects are evident in children perinatally exposed to DDT (WHO, 2010). Three different observational studies of children found an association between higher DDT exposures and lower child development scores up to four years of age. DDE exposure was also found to have associations in two of the studies; however, the findings were less consistent for DDE (WHO, 2010). Associations were reported between the DDE and PCB exposure in children (607 participants, 7-11 years old) and attention deficit hyperactivity disorder (ADHD) (Sagiv et al., 2010).

Endocrine: Several human studies were identified that demonstrated an association between DDT or DDE exposure and an increased in type 2 diabetes (WHO, 2010). Most of these studies cannot distinguish if metabolic changes due to type 2 diabetes cause higher blood levels of DDT and DDE, or if the DDE and DDT are contributing to the occurrence of diabetes. Two studies of high end fish consumers that did not have diabetes at the start of the study found that the participants that developed diabetes had higher levels to DDE (Rignell-Hydbom et al., 2009; Turyk et al., 2009). The Turyk et al (2009) study was conducted in the Great Lake Region. While the existing

literature is not conclusive with regards to the association between DDE and diabetes (WHO, 2010), there is some evidence that DDE exposure may contribute to the incidence of diabetes.

Observational studies of the people exposed to low-levels of DDT or DDE have largely found no consistent relationship with thyroid hormone status (WHO, 2010). In a study of 341 adult men with background exposures to DDT and DDE, a positive association existed between DDE and both free T_4 and total T_3 and a negative association between DDE and thyroid stimulating hormone (TSH) (Meeker et al., 2007). However, the participants had background exposures to several other chlorinated organic chemicals, of which at least two other chemicals may contribute to thyroid hormone effects.

Selection of the MDCH DDT Reference Dose (RfD)

The EPA chronic RfD and the ATSDR minimal risk level (MRL) for DDT are derived from experimental animal studies. These agencies found human studies were insufficient to be the basis of these values.

The EPA chronic RfD is an estimate of a daily oral exposure for a chronic duration (up to a lifetime) to the human population (including susceptible subgroups) that is likely to be without an appreciable risk of adverse health effects over a lifetime. The RfD for DDT is derived from a study of lesions in rat livers (Laug et al., 1950). This study was selected because it was of sufficient duration, established the male rat as the most sensitive animal, and had doses over the range of the dose-response curve (EPA, 1996). A no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) could be determined from this study (EPA, 1996).

Male and female weanling rats were fed diets containing 0, 1, 5, 10 or 50 parts per million (ppm) of commercial DDT for 15-27 weeks. No acute toxicity was observed. Histological evaluation of livers showed centrilobular hepatic cell enlargement at doses of 5 ppm and above, particularly in male rats. The authors of the study concluded that this endpoint represents the most sensitive histologically identifiable effect (Laug et al., 1950; EPA, 1996). The no observed effect level was identified as 1 ppm, which is equivalent to 0.05 mg/kg-day. EPA applied a 100-fold uncertainty factor (10 for extrapolation from animals to humans and 10 for human variability), resulting in an RfD of $5x10^{-4}$ mg/kg-day (EPA, 1996).

The ATSDR MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure. For each chemical, ATSDR may develop three MRLs: acute for one to14 days of exposure; intermediate for 15 to 364 days of exposure; and chronic for up to a lifetime of exposure. For DDT, ATSDR provides an acute and intermediate MRL, but does not calculate a chronic MRL. ATSDR refers back to the intermediate MRL stating that none of the animal studies were adequate to describe the dose-response relationship for chronic low-dose exposures. According to ATSDR, the closest acceptable study for a chronic MRL would not result in a

substantially different value than the intermediate MRL. The acute and intermediate ATSDR MRLs and the EPA RfD for DDT are the same value ($5x10^{-4}$ mg/kg-day).

ATSDR's acute MRL is based on a group of studies by the same authors that show consistent neurodevelopmental effects of DDT exposure. Mice were dosed at 10 days of age, a critical time of brain development in mice, and then tested for behavioral changes at 4 months of age. DDT exposed mice showed increased spontaneous motor activity, hyperactivity, and increased difficulty learning a new skill. The LOAEL of 0.5 mg/kg-day corresponding to the increase in spontaneous motor activity was selected. ATSDR applied a 1000-fold uncertainty factor (10 for use of a LOAEL, 10 extrapolation from animals to humans and 10 for human variability), resulting in an acute MRL of $5x10^{-4}$ mg/kg-day (ATSDR, 2002).

The intermediate MRL is based on liver effects and relies on the same study (Laug et al., 1950) used by the EPA. ATSDR selected the same point of departure concentration and applied the equivalent adjustment for uncertainty (100 total uncertainty factor), resulting in an intermediate MRL of $5x10^{-4}$ mg/kg-day (ATSDR, 2002).

DDT, DDD, and DDE are classified as probable human carcinogens. Human data have been considered inadequate for estimating cancer risk. The EPA combined the results of six liver tumor mouse datasets with individual slope factors ranging from 0.082 to 1.04 $(mg/kg\text{-}day)^{-1}$. The geometric mean of the individual slope factors was identified as the oral cancer slope factor for DDT of 0.34 $(mg/kg\text{-}day)^{-1}$.

DDT has been shown to be a tumor promoter and genotoxicity studies were mostly negative or inconclusive at the time the EPA calculated the oral cancer slope factor (EPA, 1996). Recent studies suggest further research may be warranted regarding genotoxicity. Even if genotoxic effects exist, it does not mean that mutagenic effects will occur. Thus a chemical can be genotoxic without being mutagenic.

DNA damage was documented in peripheral blood mononuclear cells (PBMC) collected from adults and children exposed to DDT and DDE (Perez-Maldonado et al., 2011; Perez-Maldonado et al., 2006; Perez-Maldonado et al., 2005). Children with greater exposure to DDT and DDE also had the greatest amount of measured DNA damage (Perez-Maldonado et al., 2011). *In vitro* assays exposing human lymphocytes to DDT or DDE have been shown to cause DNA damage (Gajski et al., 2007; Ennaceur et al., 2008). The mechanism by which this DNA damage occurs is not known, however, *in vitro* assays with human PBMCs found exposure to DDT and DDE can increase the level of reactive oxygen species (ROS) (Perez-Maldonado et al., 2005). These new studies demonstrate an increased level of uncertainty about the previous determinations regarding the genotoxicity of DDT and its metabolites. Even with these more recent studies, DDT or its metabolites are still considered inconclusive as to the genotoxic effects (ATSDR, 2002; WHO, 2010), however they do demonstrate that the current understanding is open to further study and the existing database is incomplete.

Given that DDT and DDE are cancer promoters and not initiators, these chemicals have a threshold and a non-linear dose response. An RfD approach may be used for carcinogens that have a mode of action that is nonlinear (EPA, 2005). RfDs derived from a point-of-departure based on carcinogenic effects (0.0026 to 0.057 mg/kg/d) are greater than the EPA non-cancer RfD (0.0005 mg/kg/d) (Table 2). The EPA RfD is based on morphological changes in the liver, which can be a precursor to cancer.

In addition, the EPA recommends the quotient (i.e., Margin of Exposure (MOE)) of the dose from the cancer study used to derive the cancer RfD, called the point of departure (POD), and the non-cancer RfD be large. The MOE is large for each comparison between the EPA RfD and the point of departure (POD) derived from each study (Table 2). For DDT and DDE, the use of a non-cancer RfD appears to be protective of carcinogenic effects.

Due to the incomplete database regarding genotoxicity, an additional uncertainty factor of $10^{0.5}$ (rounded to 3) was applied to the EPA RfD ($5x10^{-4}$ mg/kg-day), resulting in a final MDCH RfD of $1.7x10^{-4}$ mg/kg-day. The MDCH RfD applies to the combined exposure to DDT and its metabolites through fish consumption. The estimated maximum cancer risk for a 30- to 70- year exposure duration is between 2 to 6 additional cancers for every 100,000 exposed individuals.

Table 2. Cancer-based reference doses (RfD) for DDT and DDE compared to the EPA non-cancer RfD.

Reference	Species, Tumor, Sex	POD[a] mg/kg/d	Uncertainty Factors[e]	Cancer RfD[i] mg/kg/d	EPA RfD[j] mg/kg/d	MOE[k]
DDT						
Terracini et al. 1973	Mouse liver male & female	LOAEL[b] 33 NOAEL[c] 2.6	AH[f] – 10 HV[g] – 10	0.026	0.0005	5,200
Turusov et al. 1973	Mouse liver male & female	LOAEL 1.3 NOAEL 0.26	AH – 10 HV – 10	0.0026	0.0005	520
NCI 1978	Mouse liver male & Female	LOAEL NA[d] NOAEL 5.7	AH – 10 HV – 10	0.057	0.0005	11,400
Cabral et al. 1982	Rat liver female	LOAEL 6 NOAEL NA	AH – 10 HV – 10 UL[h] - 10	0.006	0.0005	12,000
DDE						
NCI 1978	Mouse liver male & female	LOAEL 19 NOAEL NA	AH – 10 HV – 10 UL - 10	0.019	0.0005	38,000
Rossi et al.	Hamster liver male & female	LOAEL 40 NOAEL NA	A:H – 10 HV – 10 UL - 10	0.040	0.0005	80,000

[a] POD: Point of departure which is the dose in milligrams per kilogram of DDT or DDE given each day to the animal that is used to derive the cancer RfD. The POD will default to the NOAEL, if available, otherwise the LOAEL is used as the POD.
[b] LOAEL: lowest observed adverse effect level.
[c] NOAEL: no observed adverse effect level.
[d] NA: no value could be derived from the study.
[e] Uncertainty Factors: Factors of 10 that are multiplied together, such as 10 x 10 = 100, then used to calculate the RfD (POD ÷ 100 = RfD).
[f] A:H: Animal to Human adjustment factor; applied when using animal studies to derive an RfD.
[g] HV: Human variability adjustment factor to address variation in response between people.
[h] UL: Use of a LOAEL adjustment factor to address when a NOAEL was not available and a LOAEL was used to derive the RfD.
[i] Cancer RfD: Reference dose (RfD) derived from the animal cancer study by dividing the POD by the product of the uncertainty factors.
[j] EPA RfD: Reference dose derived by the US Environmental Protection Agency (EPA) for DDT and is the RfD used by MDCH to evaluate the combined exposure of DDT, DDE, and DDD.
[k] MOE: Margin of exposure that is calculated by dividing the POD by the EPA RfD resulting in a quotient that is the fold difference between the two values. A MOE that exceeds the product of the uncertainty factors is considered large and that the RfD is protective of the endpoint.

Children's Health Considerations

Child development may be altered from exposure to DDT and DDE at an early age. Three different observational studies of children found an association between higher DDT exposures and lower child development scores up to four years of age. DDE exposure was also found to have associations in two of the studies, however, the finding were less consistent for DDE

(WHO, 2010). DDE and PCB exposure in children (607 participants, 7-11 years old) was associated with attention deficit hyperactivity disorder (ADHD) (Sagiv et al., 2010).

A study of three-hundred fifty boys between the ages of eight and nine years old were found to have exposure to mixtures of organochlorines, including DDE. The mixture exposure of DDE and other organochlorines was associated with significantly lower mean body mass index; increased DDE exposure was associated with significantly lower mean height (Burns et al., 2012). Epidemiology studies provide mixed but supportive evidence for an association between early life exposures to DDE and reduced childhood or pubertal growth (WHO, 2010).

A prospective study of prenatal exposure to DDE, DDT, and PCBs reported non-dose response associations between DDE and being overweight (Valvi et al., 2012). Difference existed between boys and girls. The increased risk of being overweight was significantly higher in the third tertile of PCB exposure [RR = 1.70; 95% confidence interval (CI): 1.09, 2.64] and the second tertile of DDE exposure (RR = 1.67; 95% CI: 1.10, 2.55), but no association with DDT exposure in the overall population.

Even beyond fetal exposure, DDT and DDE may impact the normal development of children. The *Child Health and Development* study, a longitudinal cohort study in California, found that prepubertal exposure to p,p'-DDT was correlated with increased incidence of breast cancer (Cohn et al, 2007). Public health actions, such fish consumption guidelines to minimize exposures to DDT and DDE, are necessary to allow children to get the benefits of eating fish and limit the risks.

Conclusions

MDCH concludes that eating unlimited amounts of certain sport-caught fish from lakes in Michigan throughout the year could harm people's health. This is a public health hazard. Fish consumption advisories may be required for certain fish species at specific locations. Too frequent of consumption of filets contaminated with DDT and its metabolites increases both cancer and non-cancer risks for the consumer.

Recommendations

Use the proposed RfD to develop updated DDT fish consumption screening values (FCSV) and utilize these values to provide fish consumption advice in Michigan.

Continue monitoring of sport-caught fish in Michigan for DDT.

Provide the Fish and Wildlife Contaminant Advisory Committee (FAWCAC) and other relevant groups (Great Lakes Sport Fish Advisory Task Force and Great Lakes Human Health Network) with a copy of this document.

Public Health Action Plan

1. MDCH will issue advisories in the Michigan's *Eat Safe Fish Guidelines* using updated DDT FCSVs.

2. The MDCH Analytical Chemistry Laboratory will continue to analyze fish filets, collected for the Michigan Fish Contaminant Monitoring Program (MFCMP) (administered by the Department of Environmental Quality).

3. MDCH will share a copy of this document on the internet so that FAWCAC and other relevant groups will have this information.

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