HEALTH CONSULTATION

Technical Support Document for a Reference Dose for dioxin-like chemicals (polychlorinated dibenzo-p-dioxins, dibenzofurans, and some polychlorinated biphenyls) as the Basis for Michigan Fish Consumption Screening Values

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Agency for Toxic Substances and Disease Registry

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Acronyms and Abbreviations

AhR	Aryl hydrocarbon receptor
ATSDR	Agency for Toxic Substances and Disease Registry
b-TSH	Blood- thyroid-stimulating hormone
CDD	Chlorinated Dibenzo-p-dioxins
CSF	Cancer Slope Factor
DHHS	Department of Health and Human Services
DLCs	Dioxin-like chemicals
EPA	United States Environmental Protection Agency
FAWCAC	Fish and Wildlife Contaminant Advisory Committee
FCSVs	Fish Consumption Screening Values
LD_{50}	Lethal dose to 50 percent of test animals
LOAEL	Lowest observed adverse effect level
IARC	International Agency for Research on Cancer
MDCH	Michigan Department of Community Health
MFCAP	Michigan Fish Consumption Advisory Program
MFCMP	Michigan Fish Contamination Monitoring Program
NOAEL	No observed adverse effect level
µU/ml	micro units per milliliter
MRL	Minimal Risk Level
ng/kg-day	nanograms per kilogram-day ng/kg-day
NAS	National Academy of Sciences
NTP	National Toxicology Program
pg-TEQ/g	Picograms of toxic equivalents per gram of fish tissue
ppt	parts per trillion
PCBs	Polychlorinated Biphenyls
POD	Point of departure
RfD	Chronic oral reference dose
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TEF	Toxic equivalency factors
TEQ	Toxic equivalent concentration
WHO	World Health Organization
UF	Uncertainty Factor

Disclaimer

This technical support document includes and relies on scientific information that was not available to the Agency for Toxic Substances and Disease Registry (ATSDR) when the Toxicological Profile for chlorinated dibenzo-p-dioxins was finalized. This document is not intended to replace the ATSDR Minimal Risk Level (MRL) or recommendations.

Summary

The Michigan Department of Community Health (MDCH) issues fish consumption guidelines for fish caught from Michigan waters. A group of polychlorinated dibenzo-p-dioxins, dibenzofurans, and dioxin-like polychlorinated biphenyls (PCBs), commonly referred to as dioxin-like chemicals (DLCs), are found in fish collected from some Michigan surface waters. Exposure to DLCs has been linked to numerous human health effects including cancer, altered thyroid function, developmental and reproductive effects, and diabetes.

In 2012, the United States Environmental Protection Agency (EPA) developed an oral reference dose (RfD) for the non-cancer effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which is considered to be the most toxic of the DLCs. An RfD is defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

MDCH reviewed the EPA RfD to determine if changes to the Michigan Fish Consumption Advisory Program (MFCAP) are needed to ensure that the consumption advice remains protective of public health. MDCH also reviewed the EPA's toxic equivalence (TEQ) concentration methodology for evaluating the human health risks from exposures to complex mixtures of DLCs in environmental media including fish.

MDCH's conclusion about the EPA oral RfD for TCDD:
MDCH concurs with the EPA that the RfD of 7.0×10^{-10} mg/kg-day is appropriate for TCDD.

MDCH's conclusion about the EPA TEQ methodology:
MDCH concurs with the TEQ approach for evaluating the human health risks of exposure to mixtures of DLCs found in fish. Further, MDCH concurs with the use of the toxic equivalency factors (TEF) values for TCDD and other DLCs published in 2005 by the World Health Organization as recommended by the EPA and the National Academy of Sciences.

Next steps:
The Michigan Fish Contamination Monitoring Program (MFCMP) will continue to monitor DLC levels in Michigan sport-caught fish.

MDCH will implement changes to the MFCAP and develop updated fish contaminant screening values (FCSVs) for DLCs.

MDCH will use the TEQ approach including the WHO 2005 TEFs to calculate total dioxin TEQ concentrations in fish tissue samples to identify fish consumption advice protective of public health.

Purpose and Health Issues

MDCH is in the process of updating the FCSVs used in the MFCAP. DLCs are found in fish collected from some Michigan surface waters, particularly the Great Lakes and connecting waters. Exposure to DLCs has been linked to numerous human health effects, including cancer, altered thyroid function, developmental and reproductive effects, and diabetes. The purpose of this document is to review the EPA RfD and the TEQ approach to determine if changes should be recommended to the MFCAP to ensure that the consumption advice remains protective of public health.

Background

Dioxins and dioxin-like compounds are a group of chlorinated chemicals with similar structures and chemical properties that includes polychlorinated dioxins, furans, and some polychlorinated biphenyls (PCBs). They are often referred to collectively as "dioxins" or "dioxin-like compounds" or DLCs, as they are found in the environment as a mixture of several of these chemicals. DLCs are not intentionally produced and have no known use. Not all DLCs have the same toxicity or ability to cause illness and adverse health effects. However, it is likely that all DLCs cause adverse health effects through a similar biologic mechanism of action. The available science indicates that TCDD is the most toxic chemical in the group and that the health effects resulting from exposure to multiple DLCs are additive.

Discussion

Environmental Contamination

Between 2002 and 2012, DLC concentrations were measured in 275 fish samples from 11 waterbodies and nine species following the EPA methodology (EPA 2010). DLC concentrations in edible fish tissue (i.e., fillets) ranged from 0.2 to 193 parts per trillion DLC toxic equivalents (ppt-TEQ) (Table 1). DLC concentrations in the United States food supply are typically below 1 ppt-TEQ (NAS 2003).

DLC contamination in Michigan surface waters results from the combination of atmospheric deposition and point source releases. Large, deep and cold waters, such as the Great Lakes, retain chemical contamination for a longer period of time, which results in greater accumulation of DLCs in the aquatic biota. Historical disposal practices introduced DLC contaminated wastes directly into some Michigan rivers and impoundments. Regulatory and permitting programs that place restrictions on current emissions and releases as well as remedial actions to address historical sites of contamination have greatly reduced the input of DLCs into Michigan surface waters. A decreasing temporal trend in DLC concentrations has been documented in several Great Lakes fish species (DEQ 2008, Chang et al. 2012).

Table 1. Minimum, maximum and mean TEQ concentrations in parts per trillion (ppt-TEQ) found in fish species from Michigan waterbodies sampled between 2002 and 2012.

Species	Waterbody	Number of Samples	Minimum (ppt-TEQ[a])	Maximum (ppt-TEQ[a])	Mean (ppt-TEQ[a])
Carp	Cass River	9	0.2	20.0	6.1
Carp	Detroit River	19	2.0	37.8	13.7
Carp	Kalamazoo River	21	1.7	21.8	8.9
Carp	Lake Erie	12	2.0	193.4	49.4
Carp	Lake Huron	9	7.3	117.6	46
Carp	Saginaw River	10	2.1	128.7	33
Channel Catfish	Cass River	9	1.9	17.7	5.8
Channel Catfish	Detroit River	17	4.9	104.8	27.8
Channel Catfish	Lake Erie	19	3.0	49.5	18.2
Channel Catfish	Lake Huron	10	8.7	21.5	15.8
Channel Catfish	Lake St. Clair	9	1.6	84.4	14.7
Lake Sturgeon	Lake Michigan	2	9.4	9.5	9.4
Lake Trout	Glen Lake	9	5.6	19.2	11
Lake Trout	Lake Michigan	10	9.2	49.1	23
Lake Trout	Torch Lake	11	8.3	75.7	42.7
Lake Whitefish	Lake Huron	10	4.1	17.7	8.4
Northern Pike	Detroit River	10	2.1	4.2	2.9
Walleye	Detroit River	10	1.4	18.6	5.2
Walleye	Lake Huron	20	1.4	39.2	6
White Bass	Detroit River	10	10.1	33.4	17.4
White Bass	Lake Erie	10	1.9	19.6	7.4
White Bass	Lake Huron	20	2.6	64.9	14.1
Yellow Perch	Lake Huron	9	0.3	4.1	1.2

[a] TEQ concentrations include dioxins, furans, and dioxin-like PCBs as described by EPA 2010.

Exposure Pathways Analysis

To determine whether persons are, have been, or are likely to be exposed to contaminants, MDCH evaluates the environmental and human components that could lead to human exposure.

An exposure pathway contains five elements:

- a source of contamination
- contaminant transport through an environmental medium
- a point of exposure
- a route of human exposure
- a receptor population

An exposure pathway is considered complete if there is evidence, or a high probability, that all five of these elements are, have been, or will be present at a site. It is considered either a

potential or an incomplete pathway if there is a lower probability of exposure or there is no evidence that at least one of the elements above are, have been, or will be present.

Table 2. Exposure pathway for human exposure to dioxin-like chemicals (DLCs) in fish.

Source	Environmental Medium	Exposure Point	Exposure Route	Exposed Population	Time Frame	Exposure
Atmospheric deposition, non-point source runoff, or point-source release of DLCs into Michigan Waters	Fish (contamination from the water and sediments magnifying in the food web)	Great Lakes, Inland Lakes and River Fish	Ingestion	Anyone who eats Great Lakes, inland lakes, or river fish (residents and tourists)	Past Present Future	Complete Complete Complete

Toxicological Evaluation

Toxicokinetics

TCDD is readily absorbed from food, including fish, with absorption estimated to be greater than 87 percent (EPA 2012, ATSDR 1998). Absorbed TCDD accumulates in fat over time and is very slowly eliminated from the body. The rate of elimination or half-life of TCDD in adults is between 5 to 10 years (EPA 2012, ATSDR 1998), with adult men showing generally shorter half-lives than adult women, and children exhibiting a shorter half-life than adults (EPA 2012).

The half-life for elimination of TCDD is very different between humans and animals. The EPA therefore decided that the standard scaling for interspecies extrapolation (i.e., the application of uncertainty factors to an administered dose to account for differences between animals and humans) was not appropriate. Instead, EPA used toxicokinetic modeling to estimate an effective internal dose of TCDD that would apply across all species (EPA 2012). Because TCDD accumulates in body fat, the internal dose, also called the "body burden" is expressed in units of TCDD per unit of body fat. The concentration of TCDD in blood lipids is used as a surrogate for body fat concentrations because the concentration of TCDD in blood lipids is assumed to be at equilibrium with body fat.

EPA RfD for TCDD

There is a wealth of scientific information concerning the potential health effects of exposure to DLCs, much of which has already been summarized by the ATSDR in the Toxicological profile for Chlorinated Dibenzo-p-dioxins (CDDs) (ATSDR 1998), Addendum to the Toxicological Profile for Chlorinated Dibenzo-p-dioxins (ATSDR 2012) or by the EPA in the *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* (EPA 2012). The current document will focus on the two key studies relied upon by the EPA to identify an oral RfD for TCDD.

When available, human data are generally preferred to that from animal studies when evaluating the adverse health effects of human exposure to environmental contaminants. In addition, non-occupational data are preferred when evaluating potential effects in the general human population that includes sensitive subgroups such as children. In 1976, an explosion at a trichlorophenol plant in Seveso, Italy, that released several kilograms of TCDD and

contaminated a large populated area provided a unique, albeit unfortunate, opportunity to assess the effects of dioxin exposure on human health. To develop an RfD for TCDD, the EPA relied upon two co-critical human studies that demonstrated altered thyroid function (Baccarelli et al, 2008) and impaired adult male reproductive function (Mocarelli et al, 2008) in the exposed Seveso population.

Animal studies suggest that development of the male reproductive system is a sensitive target for DLC effects (Bell et al. 2007a, 2007b). Studies of these effects in Seveso males exposed as children or young adults confirm that the human male reproductive system is similarly sensitive. Mocarelli et al. studied three age groups 22 years after the Seveso accident: infancy/prepuberty age 1-9 years, puberty age 10-17 years, and adult age 18-26 years. Men who were exposed before puberty showed reductions in sperm concentration, progressive motility, and total motile sperm count, as well as increased levels of estradiol and follicle-stimulating hormone. These effects were seen at 1976 blood levels of 68 parts per trillion (ppt) TCDD; the median blood level of the first quartile of men exposed at age 1-9 years. Men who were exposed at ages 10-17 years showed opposite effects including increased sperm counts, total motile sperm count, and FSH; and decreased estradiol. Effects seen in the two younger age groups persisted into adulthood despite a return to background TCDD levels in blood serum by 1998. Men who were exposed as adults showed no effects on these measures (Mocarelli et al. 2008). This study demonstrates that effects of DLCs on the developing male reproductive system are permanent and measurable in adulthood even when blood levels had returned to concentrations consistent with background levels. Once established, the male reproductive system appears to be less sensitive to the effects of DLCs.

Exposure to TCDD at Seveso is best described as a high initial peak exposure followed by an extended elimination period over several years during which only additional background exposure is added. It is not clear, therefore, if the effects seen in Mocarelli 2008 are associated with the peak exposure following the explosion or to the average exposure over the subsequent years of elimination. EPA used a human toxicokinetic model to calculate an oral exposure of 0.032 nanogram per kilogram-day (ng/kg-day) associated with the lowest effective peak TCDD serum concentration in Mocarelli of 68 ppt TCDD. Then, starting with the peak exposure and accounting for background exposure, the average daily serum TCDD level and an associated oral exposure of 0.0080 ng/kg-day was estimated over a five year period. Based on these values, EPA calculated an average lowest observed adverse effect level (LOAEL) of 0.020 ng/kg-day as the point of departure (POD) for Mocarelli 2008.

Neonatal thyroid function may also be a sensitive target for DLC effects related to maternal exposure. Changes in neonatal (around the time of birth) thyroid hormone function may result in long term effects including cognitive disability and neurodevelopmental impairment (Giacomini et al. 2006).

Baccarelli et al. (2008) assessed thyroid function in 1,014 children born between 1994 and 2005 to women who were of reproductive age and lived in the two zones of highest contamination (A and B) at the time of the Seveso accident. Thyroid function in these children was compared to that of children from an uncontaminated reference area. Blood thyroid-stimulating hormone (b-TSH) at levels greater than 5 micro units per milliliter of blood (μU/ml) is an indication of low

thyroid function. The mean b-TSH levels were 0.98 µU/ml, 1.35 µU/ml, and 1.66 µU/ml for the reference area, zone B and, zone A respectively. The percentage of children in the reference area whose b-TSH exceeded 5 µU/ml was 2.8, in Zone B the percentage was 4.9, and in Zone A the percentage was 16.1. In addition, the relationship of b-TSH levels in children to current TCDD levels in the mothers was studied in 51 mother-child pairs. Neonatal b-TSH levels were found to be positively correlated with current TCDD levels in the blood of the mothers (Bacacarelli et al. 2008).

EPA used the regression model developed by Baccarelli et al. 2008 to estimate a maternal plasma TCDD concentration at which neonatal TSH levels exceeded the level of concern of 5 µU/ml. EPA then used the human toxicokinetic model under the human gestational scenario to estimate a daily oral exposure that would result in a maternal TCDD serum level corresponding to a neonatal TSH of 5 µU/mL at the end of gestation. EPA identified the resulting LOAEL for maternal intake of 0.024 ng/kg-day as the POD for Baccarelli et al. 2008.

EPA determined that these two studies constitute the best foundation for establishing a POD for an RfD for TCDD and designated increased b-TSH in neonates in Baccarelli et al. (2008) and male reproductive effects (decreased sperm count and motility) in Mocarelli et al. (2008) as co-critical effects. EPA identified the slightly lower LOAEL of 0.020 ng/kg-day from Mocarelli et al. as the POD and applied a total uncertainty factor (UF) of 30: 10 for the use of a LOAEL rather than a no observed adverse effect level (NOAEL) and 3 to account for human variability. The resulting RfD is 7×10^{-10} mg/kg-day.

Fish Contaminant Screening Values (FCSVs) for DLCs

MDCH has reviewed and concurs with the rationale used by the EPA to develop an RfD for TCDD. MDCH used the TCDD RfD along with the TEQ Methodology described below to establish the FCSV for DLCs shown in Table 3.

Table 3. State of Michigan Fish Consumption Screening Values for Dioxin-like Chemicals

Meal Category	**FCSV Ranges**
meals per month[a]	*pg TEQ/g (ppt-TEQ)*[b]
16	≤ 0.5
12	>0.5 to 0.6
8	>0.6 to 0.9
4	>0.9 to 1.9
2	>1.9 to 3.7
1	>3.7 to 7.5
6 meals per year	>7.5 to 15
Limited	>15 to 90
Do Not Eat	>90

[a] Units are in months unless otherwise stated

[b] Picograms of toxic equivalents per gram of fish tissue (pg-TEQ/g) that is the same as parts per trillion (ppt-TEQ).

Background Exposures

As in most developed countries, the Seveso population likely experienced exposures to a mixture of DLCs prior to and following the accident that resulted in a peak exposure to TCDD (EPA 2012). A comparison of the calculated body burden level of non-TCDD DLCs in women in Baccarelli et al 2008 to that of U.S. adults in the mid-1990s suggests that the subjects of both the Mocarelli et al and Baccarelli et al studies had exposure to background concentrations of non-TCDD TEQ that were above current measured or expected levels (DEQ 2012). As the EPA RfD developed from these studies considers TCDD exposure only, without consideration of other DLC exposure, it is not appropriate to adjust the non-cancer FCSVs to account for additional background exposures.

Cancer Risk Considerations

EPA is currently assessing the cancer potency of TCDD (EPA 2012). TCDD has been demonstrated to be a potent cancer promoter, but is likely a weak or non-initiator of cancer (ATSDR 1998). Genotoxicity and mutagenicity studies using animal models have yielded primarily negative results therefore there is a lack of supporting evidence to conclude that TCDD is genotoxic or mutagenic (ATSDR 1998). Attachment A provides a further discussion of the available literature regarding the association of TCDD and cancer incidence.

MDCH used the Michigan Department of Environmental Quality (MDEQ) cancer slope factor (CSF) for TCDD of 75,000 $(mg/kg\text{-}day)^{-1}$ to calculate an upper-bound cancer risk associated with the FCVS and meal categories shown in Table 3. At these rates of exposure, between two and 10 additional cancers above the background incidence may occur in every 100,000 individuals exposed for 30 to 70 years, respectively. Therefore, the non-cancer FCSVs appear to be adequately protective of the cancer risk of exposure to DLCs in fish.

TEQ Methodology

The World Health Organization (WHO) developed toxic equivalency factors (TEF) to compare the relative toxicity of other DLCs to that of TCDD, which is considered the most toxic of the group. The levels of other DLCs measured in the environmental or biologic samples are multiplied by a chemical-specific TEF to produce a TCDD toxic equivalent or TEQ concentration. The resulting TEQs for all DLCs measured in a sample are then added together to determine the total dioxin TEQ concentration for that sample.

In 2005, the WHO International Programme on Chemical Safety expert panel reevaluated the TEFs for dioxins, furans, and some PCBs. Previously, TEFs were based on an arithmetic scale and assigned increments of 0.01, 0.05, 0.1, etc. However, the WHO expert panel decided to use a logarithmic scale for the 2005 reevaluation and assigned TEFs of 0.03, 0.1, 0.3 and so on based on an assessment of the available literature, which included information that had become available since the 1998 TEFs were established (Van den Berg et al. 2006). Table 4 provides the WHO 2005 TEFs.

Table 4.World Health Organization 2005 toxicity equivalence factors (TEFs) for human health risk assessment of polychlorinated dibenzo-p-dioxins, dibenzofurans, and dioxin-like polychlorinated biphenyls.

Dioxin-like Chemical	TEF
Polychlorinated dibenzo-p-dioxins	
2,3,7,8-tetrachlorodibenzo-p-dioxin	1
1,2,3,7,8-pentachlorodibenzo-p-dioxin	1
1,2,3,4,7,8-hexachlorodibenzo-p-dioxin	0.1
1,2,3,6,7,8-hexachlorodibenzo-p-dioxin	0.1
1,2,3,7,8,9-hexachlorodibenzo-p-dioxin	0.1
1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin	0.01
octachlorinated dibenzo-p-dioxin	0.0003
Polychlorinated dibenzofurans	
2,3,7,8- tetrachlorinated dibenzofuran	0.1
1,2,3,7,8- pentachlorinated dibenzofuran	0.03
2,3,4,7,8- pentachlorinated dibenzofuran	0.3
1,2,3,4,7,8- hexachlorinated dibenzofuran	0.1
1,2,3,6,7,8- hexachlorinated dibenzofuran	0.1
1,2,3,7,8,9- hexachlorinated dibenzofuran	0.1
2,3,4,6,7,8- hexachlorinated dibenzofuran	0.1
1,2,3,4,6,7,8- heptachlorinated dibenzofuran	0.01
1,2,3,4,7,8,9- heptachlorinated dibenzofuran	0.01
octachlorinated dibenzofuran	0.0003
Polychlorinated biphenyls	
3,3',4,4'- tetrachlorinated biphenyl	0.0001
3,4,4',5- tetrachlorinated biphenyl	0.0003
3,3',4,4',5- pentachlorinated biphenyl	0.1
3,3',4,4',5,5'- hexachlorinated biphenyl	0.03
2,3,3',4,4'- pentachlorinated biphenyl	0.00003
2,3,4,4',5- pentachlorinated biphenyl	0.00003
2,3',4,4',5- pentachlorinated biphenyl	0.00003
2',3,4,4',5- pentachlorinated biphenyl	0.00003
2,3,3',4,4', 5 - hexachlorinated biphenyl	0.00003
2,3,3',4,4',5'- hexachlorinated biphenyl	0.00003
2,3',4,4',5,5'- hexachlorinated biphenyl	0.00003
2,3,3',4,4',5,5'- heptachlorinated biphenyl	0.00003

The National Research Council of the National Academies of Science (NAS) reviewed the TEF approach as part of its Evaluation of the EPA reassessment of the health risks from dioxins and related compounds (Dioxin Reassessment). The NAS committee concluded that “the toxic equivalency factor methodology provides a reasonable, scientifically justifiable, and widely accepted method to estimate the relative potency of DLCs” (NAS 2006).

Children's Health Considerations

In general, children may be at greater risk than adults from exposure to hazardous substances at sites of environmental contamination. Children engage in activities such as playing outdoors and hand-to-mouth behaviors that could increase their intake of hazardous substances. They are shorter than most adults, and therefore breathe dust, soil, and vapors found closer to the ground. Their lower body weight and higher intake rate results in a greater dose of hazardous substance per unit of body weight.

Prenatal exposure to DLCs during key periods of growth and development could lead to malformation of organs (teratogenesis), disruption of function, and premature death (ATSDR 1998). The implication for environmental health is that children can experience substantially greater exposures to toxicants in soil, water, or air than adults can.

If mothers eat too much DLC contaminated fish during and in the years preceding pregnancy, the developing fetus can sustain permanent damage. Infants and children may also be exposed after birth to DLCs in breast milk and directly by eating contaminated fish. The EPA RfD is protective of prenatal exposure and post natal exposure of human infants and children.

Conclusions

MDCH's conclusion about the EPA oral RfD for TCDD:
MDCH concurs with the EPA that the RfD of 7.0×10^{-10} mg/kg-day is appropriate for TCDD.

MDCH's conclusion about the EPA TEQ methodology:
MDCH concurs with the TEQ approach for evaluating the human health risks of exposure to mixtures of DLCs found in fish. Further, MDCH concurs with the use of the toxic equivalency factors (TEF) values for TCDD and other DLCs published in 2005 by the World Health Organization as recommended by the EPA and the National Academy of Sciences.

Recommendations

Develop updated fish contaminant screening values (FCSVs) for DLCs.

Continue to monitor DLC levels in Michigan sport-caught fish.

Use the TEQ approach including the WHO 2005 TEFs to calculate total dioxin TEQ concentrations in fish tissue samples to identify fish consumption advice protective of public health.

Provide the Michigan 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

MDCH will implement changes to the MFCAP and develop updated fish contaminant screening values FCSVs for DLCs.

The Michigan Fish Contamination Monitoring Program (MFCMP) will continue to monitor DLC levels in Michigan sport-caught fish.

MDCH will use the TEQ approach including the WHO 2005 TEFs to calculate total dioxin TEQ concentrations in fish tissue samples to identify fish consumption advice protective of public health.

MDCH will provide the FAWCAC and other relevant groups (Great Lakes Sport Fish Advisory Task Force and Great Lakes Human Health Network) with a copy of this document.

MDCH will remain available as needed for future consultation on this issue.

If any citizen has additional information or health concerns regarding this health consultation, please contact MDCH's Division of Environmental Health at 1-800-648-6942.

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Appendix A

Supplemental Information on the Health Effects of DLCs

The discussion below is a brief review of additional information concerning the health effects of DLCs in animals and people that were reviewed and considered in the selection of key studies and health effects for the development of FCSVs for DLCs.

Health Effects in Animals

Cancer – A 2-year rat bioassay conducted by Dow in the 1970's (Kociba 1978) has been used by the EPA, the State of Michigan, and many other agencies to evaluate the cancer potency of TCDD. Most recently, the National Toxicology Program (NTP) conducted a series of four 2-year cancer bioassays of TCDD, other DLCs including PCB-126 and 2,3,4,7,8-pentachlorodibenzofuran (PeCDF), or a mixture of all three. The purpose of these studies was to replicate results seen in the earlier rat bioassay conducted by Dow and to evaluate the TEF approach used for mixtures of multiple DLCs. The 2004 NTP bioassay confirmed that exposure of female rats to TCDD resulted in increases in the incidence of cancer of the liver, lung, and oral mucosa. Some liver cancers (cholangiocarcinomas) were seen at higher rates in the NTP study than had been observed in the earlier Dow study (Walker 2006). Additionally, these cancers were significantly and dose-dependently increased in rats exposed to PCB-126, PeCDF, and to the mixture of all three DLCs. Analysis of the dose-response modeling for each DLC and the mixture confirmed that the effects of exposure to mixtures of these chemicals are additive for these cancer endpoints. Additionally, the relative potency of PCB-126 (0.1) and PeCDF (0.3) to TCDD was found to be consistent with the WHO 2005 TEF values for these DLCs (Walker 2005).

Non-Cancer – DLCs have been widely studied in a variety of animal test subjects. TCDD has been called "the most toxic man-made chemical" because it can cause death at very low doses. The dose at which TCDD causes death in 50 percent of test animals, called the LD_{50}, varies widely between species with the guinea pig likely to be the most sensitive species tested. The TCDD dose that could kill a person is not known, but three intentional attempts to poison people suggest the lethal dose for a person is far higher than that for guinea pigs (Schecter et al. 2005).

While LD_{50} values can vary widely, other adverse effects observed in test animals occur at similar doses in multiple mammalian species. Exposure of test animals to DLCs has resulted in reproductive and developmental abnormalities, immune system effects, nervous system effects, endocrine disruption, diabetes, thyroid disorders, liver damage, dental abnormalities, and blood effects such as elevated cholesterol and triglycerides (ATSDR 1998, Schecter et al 2005). Results from animal studies suggest that the perinatal period, before and just after birth, is the most critical period for DLC exposure and that the endocrine (hormonal) system is likely the most sensitive target. (Nishimura et al. 2008; Bell et al. 2007a; Bell et al. 2007b).

There is a large body of compelling information that supports the assumption that people and other mammals respond to DLCs in similar ways at the cellular level via the aryl hydrocarbon receptor (AhR). Activation of the AhR by TCDD and other DLCs that bind to it sets off a cascade of cellular events that are thought to be responsible for the health effects associated with

these compounds (Walker 2006). Therefore, it is reasonable to assume that people may experience the same health effects as those seen in studies of other mammals.

Human Health Effects

Studies of people who were exposed to high levels of DLCs at their work place, through industrial accidents, and in contamination incidents have demonstrated adverse effects, but there are not always consistent results among these studies. Only three instances of intentional human poisonings have been reported. For a severe acne-like skin condition called chloracne, the effect of dioxin exposure is obvious and occurs soon after exposure. For other effects (e.g., cancer and chronic diseases like diabetes), it may take many years before health effects, if any, are seen and it may be difficult to determine if the effect is from exposure to DLCs.

Human studies are often difficult to interpret because every person lives differently and people may be exposed to multiple chemicals at the same time. It takes a lot of exposed people in a well-designed study to see increases in common conditions such as heart disease, diabetes and some types of cancer. Recent studies that will be discussed further below confirm the need to carefully define exposure groups (e.g., non-exposed vs. highly exposed). In many older studies, people were assigned to exposure groups based on assumptions about occupational duties that could result in exposure to dioxins. More recent analysis of serum blood dioxin levels in workers revealed that high dioxin exposures may occur unexpectedly and that comparison groups must be carefully chosen based on measured dioxin body levels (Collins et al. 2005).

Some studies of exposed populations that showed little health impact or uncertain results were conducted within a few years after exposure, but many of the potential health effects of DLCs such as cancer are not seen until 15 or 20 years following exposure. Offspring of exposed people may show effects of dioxin exposure at levels that do not affect the health of the parents. More recent analysis of the data is finding significant health impacts in these exposed people.

Cancer - The WHO International Agency for Research on Cancer (IARC), the United States Department of Health and Human Services (DHHS) National Toxicology Program 9th Report on Carcinogens (NTP 2001), and the EPA have all classified TCDD as a human carcinogen. The EPA has characterized the mixture of DLCs to which people are commonly exposed as "likely to be carcinogenic to humans" (EPA 2000). The NAS, the WHO, and DHHS concur that the other DLCs and mixtures of those compounds are likely to cause cancer.

The NAS in its 2006 evaluation of the EPA Dioxin Reassessment recommended that the EPA reevaluate its conclusions regarding whether TCDD is “carcinogenic to humans” or “likely to be carcinogenic to humans.” The difference between these two conclusions relies primarily on the strength of the evidence. However, the NAS stated that the “public health implications of the two terms appeared to be identical.” This means that, regardless of the classification used, people should take precautions to limit their exposure to this chemical. Recent studies in human populations exposed to TCDD have confirmed the association of cancer incidence with dioxin exposure. The most consistent findings from human studies of TCDD exposure show an increase in all cancers combined.

In 1997, IARC classified TCDD as "carcinogenic to humans" based on limited evidence in humans, sufficient evidence in animals, and extensive evidence that TCDD acts through a similar mechanism, binding to the AhR, in both humans and animals. IARC reaffirmed this classification for TCDD in 2012 and also classified 2,3,4,7,8-pentachlorodibenzofuran and 3,3',4,4',5-pentachlorobiphenyl (PCB126) as "carcinogenic to humans." IARC relied on studies of people who were occupationally exposed to TCDD in chemical production or pesticide application as well as residents of Seveso, Italy where an accident exposed local residents (IARC 1997, IARC 2012).

In 1976, an explosion at a trichlorophenol plant in Seveso, Italy released several kilograms of TCDD and contaminated a large populated area. Studies of health effects in the exposed populations began almost immediately after the accident, however initial findings in 1984 identified only chloracne as a certain effect (Consonni et al. 2007). The Seveso population, divided into three zones of exposure, has been followed over the intervening years to assess cancer incidence and mortality. After 20 years, all cancer mortality in the most polluted area, Zone A, showed a 60 percent increase among males. Lung cancer mortality was also elevated in males in Zone A 15 years after the accident (Consonni et al. 2007). These findings are consistent with those seen in occupational studies of men exposed to TCDD at their jobs. Additionally, rectal cancer incidence and mortality was increased in males in the exposed Seveso population.

Among exposed females, liver cancer incidence was elevated in females 15 years after the accident (Steenland et al. 2004). Breast cancer incidence was found to increase 2-fold with a 10-fold increase in serum TCDD in Zone A women (Warner et al. 2002).

The Seveso population also shows an excess of lymphatic and hematopoietic neoplasms in both males and females, in both Zone A and Zone B (Consonni et al. 2007). The lymphatic system includes lymph nodes, ducts and lymph vessels, whose function is to produce and carry lymph fluid around the body. The hematopoietic system includes the bone marrow, spleen, tonsils, and lymph nodes, and is involved in the production of all types of blood cells.

More recent analyses of occupational data conducted after the 1997 IARC classification of TCDD, have relied on better methods to estimate the level of TCDD in blood serum thus allowing for more accurate predictions of the exposure-response relationship. These newer studies all benefited from the availability of measurements of serum blood TCDD levels for at least a subset of the workers, which allowed researchers to predict the blood levels in workers who had performed similar tasks for the same length of time. These analyses show an increasing risk for all cancers as exposure to TCDD increases. In a study of Dutch workers, those in the medium and high exposure groups had a 5-fold increase in cancer mortality compared with workers at the same manufacturing plant who were in the low exposure group (Steenland et al. 2004). Newer analyses of United States worker data that include several years of additional follow-up indicate a significant trend in all cancer mortality with increasing dioxin exposure (Crump 2003, Steenland 1999). A strength of these newer studies is that they compare cancer rates between the workers (who are likely to be similar in lifestyle, availability of health care, and socioeconomic class) rather than to the general population that includes the elderly and people who may be less healthy than the actively employed (Steenland et al. 2004).

During the Vietnam War, the United States Air Force used the herbicides 2,4-dichloro-phenoxyacetic acid (2,4-D) and 2,4,5-trichloropheoxyacetic acid (2,4,5-T) in an equal mixture to clear jungle foliage. This mixture, called Agent Orange because of orange labels on the containers, was contaminated with TCDD. Operation Ranch Hand was the Air Force unit that handled and loaded the Agent Orange onto aircraft, and flew those aircraft in aerial spraying missions. In 2006, the NAS Institute of Medicine concluded that there is sufficient evidence of an association between exposure to herbicides and TCDD and soft-tissue sarcoma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL), Hodgkin's disease, and chloracne. The NAS also found limited or suggestive evidence of an association of herbicide and TCDD exposure and the following: cancer of the larynx, lung, bronchus, trachea, prostate; multiple myeloma; primary amyloidosis; early-onset transient peripheral neuropathy; porphyria cutanea tarda; hypertension; Type 2 diabetes (mellitus), and spina bifida in offspring of exposed people (IOM 2007).

Recently, researchers have further defined which Vietnam veterans were most highly exposed to TCDD and examined disease incidence in veterans as a function of the timing and duration of exposure (Akhtar et al. 2004; Michalek and Pavuk 2008). Veterans' exposure was stratified by their calendar period of service (during and before 1968 or after 1968), the number of days spraying, and the duration of their service in Southeast Asia. The calendar period of service is important because TCDD contamination present in Agent Orange is thought to have been higher before 1969. The number of days spraying and the duration of service are important because people who are exposed for longer periods of time will likely have more dioxin in their bodies than people who are exposed for shorter periods of time. When the Ranch Hand veterans were stratified in this way, cancer risk estimates were significantly increased for the entire group and for the high exposure category in particular (Michalek and Pavuk 2008). These results likely differ from earlier reports because exposure was more accurately defined and because more time had elapsed since exposure.

In addition, recent studies conducted in California have confirmed the link between exposure to Agent Orange and prostate cancer in Vietnam veterans. Researchers stratified veterans receiving care at the Northern California Veteran Affairs Health System as either exposed or unexposed, and examined demographic data and prostate health status. Twice as many exposed veterans had been diagnosed with prostate cancer. In addition, exposed veterans had been diagnosed at an earlier age and were more likely to have cancer that has spread to other parts of the body (Chamie 2008).

Chloracne - This severe acne-like disease is known to be associated with high levels of exposure to DLCs. However, not everyone who is exposed to high levels will have chloracne and its absence cannot be taken as proof that no exposure has occurred. Chloracne may be disfiguring and can persist for years, sometimes clearing only to recur several years later. Workers exposed on the job; adults and especially children exposed by the accident at Seveso, Italy; and the three people known to have been intentionally poisoned with TCDD have all developed chloracne. (Schecter 2005).

Diabetes - As previously discussed, the NAS found evidence of an association of TCDD herbicide exposure and Type 2 diabetes (sometimes called adult onset diabetes) in Vietnam

veterans. Recent analysis of diabetes incidence in Operation Ranch Hand veterans provides further strength for this association when exposure is adjusted for calendar period of service and for number of days spraying Agent Orange herbicides (Michalek and Pavuk 2008).

Studies of the relationship of DLC exposure and diabetes incidence in occupational settings have yielded mixed results. Calvert et al. (2005) found that workers with very high (> 1500 ppt) serum TCDD levels were at greater risk of developing diabetes. However, no difference was found in diabetes incidence between other exposed workers with lesser TCDD levels and a referent group with TCDD serum levels below 20 ppt.

Women who had been exposed to DLCs (primarily polychlorinated biphenyls and polychlorinated dibenzofurans) during the 1970's Yucheng accidental rice oil poisoning event in Taiwan were 2.1 times more likely to develop diabetes than women in an unexposed referent group (Wang et al. 2008). Similarly, women in all exposure zones in Seveso, Italy, were found to have slightly higher mortality rates from diabetes when compared to a non-exposed population (Consonni 2008).

People who lived adjacent to a TCDD-contaminated site in Arkansas were studied by Cramer et al. (2000) to determine if blood serum levels of the DLC were associated with biomarkers of diabetes and insulin resistance. People whose blood level of TCDD was in the highest 10 percent of those studied were more likely to have higher plasma insulin concentrations after a glucose load, suggesting that higher levels of TCDD in blood serum is associated with insulin resistance.

Other researchers have used human blood serum and survey results from the National Health and Nutrition Examination Surveys (NHANES) to investigate the association between background exposures to DLCs and diabetes. These investigations are limited because only a few DLCs could be measured in the blood of many of the people who participated. Lee et al. (2006) reported that diabetes incidence was positively associated with serum lipid levels of a group of six measured pollutants that included two chlorinated dioxins.

Developmental Effects - The 1976 explosion in Seveso, Italy provides a unique, albeit unfortunate, opportunity to assess the effects of dioxin exposure on human development. Children in Seveso who were exposed to TCDD had higher levels of the DLCs in their blood compared to adults. Approximately 20 percent of exposed children developed chloracne following the accident (Alaluusua et al. 2004).

Reports on the 1970's Yucheng event in Taiwan suggested that children born to women exposed to DLCs while pregnant had dental abnormalities that persisted into adult life (Guo et al. 2003). Therefore, Seveso children who were younger than nine and a half years at the time of the accident were examined 25 year later for dental defects. People who had lived in the contaminated zones showed a higher prevalence (42%) of development defects in their tooth enamel compared to people who had not lived there (26%). People with higher serum TCDD levels as children showed these effects more often than people who had lower levels. More people from the contaminated zones (12.5%) also had missing permanent teeth than people from the non-contaminated zones (4.6%) (Alaluusua et al. 2004).

In contrast to the effects seen in the Seveso population, studies of the relationship of background DLC exposures and neonatal thyroid function have provided inconsistent results. Studies conducted in the Netherlands suggested that babies born to mothers with higher DLC blood concentrations had higher b-TSH levels at 11 weeks of age (Pluim et al. 1993), but this effect was not observed at two and half years of age, nor at 7-12 years (ten Tusscher et al. 2008). A more recent study conducted in Duisburg, Germany also failed to find any relationship between background blood DLC concentrations of 3.8 to 58.4 ppt in mothers and thyroid function or neurodevelopment in children assessed through 24 months of age (Wilhelm 2008). However, a negative association was found in the Duisburg, Germany study between maternal exposure to DLCs and sex steroids in infants as measured in cord blood (Cao et al. 2008). Studies conducted in Chapaevsk, Russia have also found alterations in male reproductive function (delayed puberty) with increased DLC blood levels in boys at ages 8-9 years old (Korrick et al. 2011, Humblet et al, 2013). A recently published study also found differences in anogential distance (considered a biomarker of reproductive function) in newborn males (Vafeiadi et al., 2013).

In addition to thyroid function, the studies conducted in the Netherlands investigated the effects of perinatal exposure to DLCs and immunological function. While no health effects were seen in infancy, DLC exposure was associated with a decrease in the number of white blood cells. Health effects were reassessed in these children at preschool age (Pluim 1994). Higher DLC exposure was associated at this age with an increased incidence of ear infections, viral diseases like chicken pox, coughing, chest congestion and phlegm. However, white blood cell numbers were found to be normal (Weisglas-Kuperus et al. 2000). At 8 years of age, children from this group were again assessed for health status and blood factors. In this report, prenatal exposure to DLCs was associated with a decrease in allergies, which may be a result of immune system impairment. Levels of blood factors were within normal ranges, however exposure to DLCs was associated with lower levels of blood clotting cells (thrombocytes and platelets) (ten Tusscher et al. 2003).

Spatial abilities are typically better developed in boys than girls. Changes in spatial abilities of male offspring born to women exposed to high levels of PCBs and furans during the Yucheng event suggests that prenatal exposure to DLCs may result in demasculinated behavior in boys (Guo et al. 2003). Additional studies conducted in the Netherlands investigated the effects of background exposures to PCBs and dioxins on play behavior at school age. Play behavior was assessed on three subscales: masculine, feminine, and composite. The results indicated an association between higher prenatal exposure to DLCs and more feminized play behavior in both girls and boys (Vreugdenhil et al. 2002). This study suggests that sex hormones (steroids) may be affected by prenatal exposure to these compounds.

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