# Discussion Paper for a Chlordane Health Protection Value (HPV)

## Great Lake Consortium for Fish Consumption Advisories

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This paper provides an overview of the toxicity of chlordane, in support of the development of a Health Protection Value (HPV) for chlordane to be used with the Protocol for Developing Great Lakes Fish Consumption Advisories. It is intended to aid discussion and development of a chlordane HPV by the members of the Great Lakes Fish Advisory Task Force (Task Force) for use with the Great Lakes states' fish consumption advisories. Included are discussions of noncarcinogenic endpoints, cancer risks, HPV issues and options, and a recommendation for the most appropriate option for adoption by the Task Force.

**NONCARCINOGENIC ENDPOINTS**

Chlordane has been shown to affect several organs/organ systems in numerous studies reported in the literature. Those organs/systems which appear to be most sensitive to chlordane toxicity have been selected for development of candidate HPVs for the Task Force's discussion.

Immune System Effects

Numerous studies have evaluated the effects of chlordane on various aspects of immune system function. Spyker-Cranmer, et al. (1982) have identified a No Observable Adverse Effect Level (NOAEL) for decreases in the cell-mediated immune response in offspring of treated female mice (with no effects on the humoral immune response) at 0.16 mg/kg/d during gestation. Conversely, Johnson, et al. (1986) have identified a NOAEL for increases in the cell-mediated response (again with no effect on the humoral response) at 4 mg/kg/d in juvenile mice dosed for two weeks beginning at age 6 weeks.

In other studies with mice dosed during gestation, Barnett et al. (1990 a, b) identified a NOAEL in offspring of 4 mg/kg/d for decreases in both granulocyte-macrophage precursors and spleen-forming and liver-forming stem cells in bone marrow; however, no effects were observed on numbers of any mature cells in these studies. Barnett, et al. (1985 a, b) reported a NOAEL of 4

mg/kg/d for decreased delayed-type hypersensitivity response, but this effect may have been protective in that these mice were found to have increased survival to an influenza virus challenge, with no effects observed on the virus-specific cell-mediated immune response. And Blaylock, et al. (1990) reported varied effects on natural killer (NK) cell responses in offspring which are difficult to interpret: decreased NK response in male offspring of 8 mg/kg-dosed dams at 200 days post-partum, but not at 100 days; increased NK response in female offspring of 8 mg/kg-dosed dams at 100 days post-partum, but not at 200 days; no response in offspring of 4 mg/kg-dosed dams; and no effect on the cell-mediated immune response, in contrast to other studies from this laboratory showing effects on cell-mediated immune responses in offspring of treated dams.

Two other studies also provide data on immune system effects which are difficult to interpret. Johnson, et al. (1987) reported a NOAEL for decreased in vitro cell-mediated and B-cell immune responses at 0.1 µM chlordane concentration, but no effects in vivo. Theus, et al. (1992) identified a Lowest Observable Adverse Effect Level (LOAEL) at 8 mg/kg/d during gestation for alteration of offspring's macrophages into inflammatory status, a response whose significance is poorly understood.

Given the somewhat confusing and even contradictory nature of the results discussed above, it is difficult to select the most appropriate study for development of a candidate HPV. Nevertheless, the decreased cell-mediated immune response reported in the offspring of dams fed 0.16 mg/kg/d during gestation (Spyker-Cranmer, et al., 1982) may be a response with biological consequences. Therefore, this study is used to develop a candidate HPV for immune system effects. The NOAEL is divided by uncertainty factors (UF) of 10 for interspecies extrapolation and 1 for intraspecies extrapolation (since the exposure and effects are reported for a sensitive population, offspring exposed during gestation), and a modifying factor (MF) of 10 for the overall weakness of the reproductive/developmental toxicity database (discussed below). Thus, the HPV is:

$$\text{HPV} = \frac{0.16 \text{ mg/kg/d}}{(10)(1)(10)} = 0.0016 \text{ mg/kg/d} = 1.6 \text{ µg/kg/d}$$

Reproductive/Developmental Effects

There is a relative paucity of information regarding the reproductive and developmental toxicity of chlordane which is surprising considering the long and widespread use of this compound. There are no studies of exposed human populations, no multigenerational animal studies evaluating reproductive effects, and only one study evaluating effects on fertility from oral

exposure. This study reported a LOAEL for decreases in numbers of litters and no survival to weaning in rats fed 16 mg/kg/d (Ambrose, et al., 1953). Several chronic/cancer bioassays have reported no histopathological lesions in the reproductive tracts of male and female rodents at maximum doses ranging from 1.175 mg/kg/d (Khasawinah and Grutsch, 1989a) to 20.4 mg/kg/d (NCI, 1977). Chlordane does not appear to cause teratogenic effects, with negative results reported at maximum doses of 50 mg/kg/d (Chernoff and Kavlock, 1982) and 80 mg/kg/d (Usami, et al., 1986).

There are several studies evaluating the developmental effects of chlordane, including the studies of immune system effects in offspring of treated dams discussed above. Al-Hachim and Al-Baker (1973) reported a LOAEL for deficits in several neonatal development markers in mice, including avoidance response, open field test, and shock seizure threshold, at 1.0 mg/kg/d. Talamantes and Jang (1977) dosed mouse pups at 0.075 or 0.15 mg chlordane/pup on days 2, 3, and 4 post-partum and found decreased growth rates and delayed eye-opening that was not dose-related. There is also one study describing effects on plasma testosterone levels in developing rats which is discussed in the section on endocrine system effects.

Exclusive of the studies reporting immune system effects, the most sensitive endpoint among the reproductive and developmental studies discussed above appears to be deficits in developmental markers (Al-Hachim and Al-Baker, 1973). This study reported a LOAEL of 1.0 mg/kg/d, from which a NOAEL is estimated by application of a UF of 10. A UF of 10 is also employed for interspecies extrapolation and a UF of 1 is used for intraspecies extrapolation since the test organisms (neonates) are considered to be a sensitive population.

In light of the overall weakness of the database for reproductive and developmental toxicity, it is appropriate to employ a modifying factor in developing the HPV for chlordane. In developing the revised Reference Dose (RfD) for chlordane, USEPA (1998) chose to use a MF of 3 to account for this weakness. However, the recently enacted Food Quality Protection Act specifies a MF of 10 to account for effects on children, including reproductive and developmental effects, unless data are sufficient to lessen this MF. Since it is not clear at this time what are the criteria for relaxation of the reproductive/developmental toxicity MF, a MF of 10 will be used throughout this paper for discussion purposes. Thus, a candidate HPV for reproductive/developmental effects is:

$$\text{HPV} = \frac{1.0 \text{ mg/kg/d}}{(10)(10)(1)(10)} = 0.001 \text{ mg/kg/d} = 1.0 \text{ µg/kg/d}$$

Nervous System Effects

In contrast to the reproductive/developmental toxicity database, there is an extensive database regarding the nervous system toxicity of chlordane. This is not surprising since nervous system effects are the basis of chlordane's insecticidal activity. Therefore, only those studies which appear to identify the most sensitive nervous system toxicity endpoints are discussed.

In a cancer bioassay with rats and mice, the National Cancer Institute identified NOAELs for tremors in rats at 6.0 mg/kg/d and mice at 3.9 mg/kg/d (NCI, 1977). Drummond, et al. (1983) reported a LOAEL for decreases in brain ATPases in rats at 1.25 mg/kg/d for 12 weeks, while Khasawinah and Grutsch (1989 b) reported no gross central nervous system symptoms or histopathological lesions in mice at doses as high as 1.21 mg/kg/d in another cancer bioassay. Thus, it appears that a NOAEL for nervous system effects in rodents is in the range of 1-6 mg/kg/d.

The study of Drummond, et al. (1983), which found a LOAEL for decreases in brain ATPases at 1.25 mg/kg/d for 12 weeks, appears to represent the most sensitive endpoint for nervous system toxicity. However, it is not clear whether this effect has biological significance, since the Khasawinah and Grutsch study (1989 b) found a NOAEL for nervous system effects at a similar dose (1.21 mg/kg/d) during a full cancer bioassay. Therefore, the Khasawinah and Grutsch study is selected as the basis for a candidate HPV. UFs of 10 are employed for inter- and intraspecies extrapolation, and a MF of 10 is used for the weakness of the reproductive/developmental toxicity database. The HPV is:

$$\text{HPV} = \frac{1.21 \text{ mg/kg/d}}{(10)(10)(10)} = 0.00121 \text{ mg/kg/d} = 1.21 \text{ µg/kg/d}$$

Endocrine System Effects

Several studies have reported effects from chlordane exposure which are endocrine-related. In addition to the immune system effects already discussed in the Spyker-Cranmer, et al. study (1982), these authors also determined a LOAEL for increased plasma corticosterone in offspring of dams dosed during gestation at 0.16 mg/kg/d, although the increases were not dose-related in female offspring. Shain, et al. (1977) reported a LOAEL for increased numbers of prostate androgen receptors in rats at 19.5 mg/kg/d.

There are three studies assessing reproductive performance which may also exhibit endocrine-related effects. The previously-discussed study by Ambrose, et al. (1953), the only oral study to

specifically address fertility effects, reported decreased fertility in rats which may be endocrine-related, with a LOAEL of 16 mg/kg/d. Balash, et al. (1987) reported a LOAEL for decreased size of seminiferous tubules and altered spermatogenesis in mice at 100 mg/kg/d. And Cassidy, et al. (1994) reported a number of subtle effects in offspring of female rats dosed during gestation and lactation, which were subsequently dosed at the same maternal level through post-lactation day 60. Among this study's findings were several improvements in dosed offspring parameters versus controls, including male mating behavior, and certain deficits in relation to controls, including a NOAEL for decreased plasma testosterone in females at 0.1 mg/kg/d (but no effect on testosterone in males) and an increase in startle response in males and females that was not dose-related.

It is somewhat difficult to select a study from which to develop a candidate HPV from the above studies, in part because of the confounding with reproductive toxicity and in part because of the questionable relevance of the findings. Nevertheless, the study of Spyker-Cranmer, et al. (1982), which found a LOAEL for increased plasma corticosterone in offspring of treated dams at 0.16 mg/kg/d, is chosen as the most sensitive measure of endocrine system toxicity in spite of the limitations of this study (no dose-response relationship in female offspring, questions regarding the relevance of this effect). A UF of 10 is used to convert the LOAEL to a NOAEL; UFs of 10 and 1 for inter- and intraspecies extrapolation and a MF of 10 for the overall weakness of the reproductive/developmental toxicity database are used as before. The candidate HPV is:

$$\text{HPV} = \frac{0.16 \text{ mg/kg/d}}{(10)(10)(1)(10)} = 0.00016 \text{ mg/kg/d} = 0.16 \text{ µg/kg/d}$$

Liver Effects

As was the case for nervous system toxicity, there are many studies reporting effects on the liver due to chlordane exposure. USEPA (1998) has reviewed this extensive database and determined that many of the studies have limitations, including high doses which produced excessive mortality or which had to be decreased during the study, studies conducted with only one dose level, and studies conducted at low doses which do not identify clearly adverse effects on the liver. Therefore, USEPA performed a Benchmark Dose analysis of the liver toxicity database, which did not acceptably model the liver toxicity of chlordane. As a result, USEPA selected the cancer bioassay of Khasawinah and Grutsch (1989 a) as the basis for developing the revised RfD for chlordane. This study found a NOAEL for liver necrosis in male mice at 0.15 mg/kg/d. USEPA employed UFs of 10 for inter- and intraspecies extrapolation and a MF of 3 for the overall weakness of the reproductive/ developmental toxicity database (without discussion

or justification for not using the 10-fold MF required by the Food Quality Protection Act) to derive the revised RfD:

$$\text{RfD} = \frac{0.15 \text{ mg/kg/d}}{(10)(10)(3)} = 0.0005 \text{ mg/kg/d} = 0.5 \text{ µg/kg/d}$$

(This RfD replaces the previous value of 0.00006 mg/kg/d = 0.06 µg/kg/d based on liver hypertrophy, which may have been an adaptive response rather than an adverse effect.) Note that if a MF of 10 is used for the overall weakness of the reproductive/developmental toxicity database for this study, as has been done for the other candidate HPVs, a candidate HPV would be:

$$\text{HPV} = \frac{0.15 \text{ mg/kg/d}}{(10)(10)(10)} = 0.00015 \text{ mg/kg/d} = 0.15 \text{ µg/kg/d}$$

As a final note regarding the toxicity of chlordane to the liver, a study by Mahon and Oloffs (1979) not included in USEPA's review, which has some limitations but which may also have relevance to the development of the HPV for chlordane, provides some perspective. This study determined a LOAEL of 0.05 mg/kg/d for increased severity of cirrhotic liver damage in rats pre-treated with carbon tetrachloride. If this study is used as the basis for a candidate HPV, using UFs of 10 for interspecies extrapolation and conversion of a LOAEL to a NOAEL, a UF of 1 for intraspecies extrapolation (since the study is of sensitive individuals by virtue of pre-existing cirrhosis), and a MF of 10 for the overall weakness of the reproductive/ developmental toxicity database, the candidate HPV would be:

$$\text{HPV} = \frac{0.05 \text{ mg/kg/d}}{(10)(10)(1)(10)} = 0.00005 \text{ mg/kg/d} = 0.05 \text{ µg/kg/d}$$

**CARCINOGENIC ENDPOINT**

USEPA (1998) has also reviewed the cancer-causing potential of chlordane in order to revise the oral slope factor for this chemical. This review determined that the weak human evidence plus the strong animal evidence classifies chlordane as a likely human carcinogen. The human evidence consists primarily of excesses of non-Hodgkins lymphoma in farmers handling insecticides (complicated by exposures to other potentially carcinogenic agents), and other reports of immune system dyscrasias in persons known to have been exposed directly to chlordane (and other potentially carcinogenic chemicals) contributes to the human evidence. The animal evidence includes large excesses of liver tumors in five strains of mice fed chlordane

(both sexes) and pre-neoplastic lesions, but no tumors, in rats. Supporting evidence is found in limited in vitro data showing genotoxic effects, and other in vitro data showing inhibition of intercellular communication, stimulation of protein kinase C, and induction of lipid peroxidation. There is uncertainty regarding whether the effects described above, which occurred at relatively high exposures or doses, can reasonably be extrapolated to predict carcinogenic risk at environmentally relevant exposures.

Since there are no reliable exposure data from the various human studies, it is not possible to develop an oral slope factor based on human data. Furthermore, there is no basis for selecting one of the five mouse bioassays reporting increased incidences of liver tumors. Therefore, USEPA derived the revised oral slope factor, 0.35 (mg/kg/d)-1, from the geometric mean of the five studies' slope factors. (Note that the previous oral slope factor was 1.3 (mg/kg/d)-1, also based on liver tumor incidence in mice.) Using this slope factor, it is possible to calculate the daily intake of chlordane corresponding to a cancer risk level from:

Daily intake (mg/kg/d) = Risk level / Slope factor [(mg/kg/d)-1]

Thus, the daily intakes corresponding to regulatorily important risk levels are:

1 in 10,000 lifetime risk = 1.0E-4 / 0.35 = 0.000286 mg/kg/d = 0.286 μg/kg/d

1 in 100,000 lifetime risk = 1.0E-5 / 0.35 = 0.0000286 mg/kg/d = 0.0286 μg/kg/d

1 in 1,000,000 lifetime risk = 1.0E-6 / 0.35 = 0.00000286 mg/kg/d = 0.00286 μg/kg/d

It is also possible to calculate the cancer risk level corresponding to a daily intake of chlordane from:

Risk level = Daily intake (mg/kg/d) x Slope factor [(mg/kg/d)-1]

As an example, the lifetime cancer risk corresponding to a daily intake equal to the revised RfD of 0.0005 mg/kg/d is:

Lifetime cancer risk = 0.0005 x 0.35 = 1.75 in 10,000 = 1.75E-4

The candidate HPV and cancer risk information is summarized in Table 1.

## HPV ISSUES AND OPTIONS

There are several issues which must be addressed in order to develop a HPV for chlordane. These issues can be best put in focus by selecting a candidate HPV for discussion purposes,

developing the five concentration ranges corresponding to the Great Lakes Protocol's consumption advice groups (using the same assumptions employed in the development of the HPV for polychlorinated biphenyl (PCBs)), and then examining the consequences of the various options presented by the issues.

Strawman HPV and Consumption Advice

For discussion purposes, the revised RfD of 0.0005 mg/kg/d will be used to derive the five fish tissue concentration ranges for the Protocol's consumption advice groups. Using the Protocol's assumptions of a meal size of one-half pound (0.227 kg), a body weight of 70 kg, and a 50% reduction of fish tissue levels due to proper cleaning and cooking of the fish, the concentration ranges of chlordane in the raw fish tissue for the five advice groups are:

Group 1 (No restriction) = 0 - 0.50 mg/kg

Group 2 (1 meal/wk) = 0.51 - 2.18 mg/kg

Group 3 (1 meal/mo) = 2.19 - 9.42 mg/kg

Group 4 (6 meals/yr) = 9.43 - 18.8 mg/kg

Group 5 (No consumption) = >18.8 mg/kg

Issues and Consequences

There are at least three important issues which must be resolved in order to determine what is the most appropriate HPV for chlordane.

1.) Cancer risk: Since the strawman consumption advice is designed to limit daily intake to no more than the strawman HPV, which is the revised USEPA RfD, there is a concern that such an advisory structure may subject sport fish consumers to unacceptable cancer risks. As illustrated above in the discussion of the carcinogenic endpoint, a daily intake equal to the RfD corresponds to a lifetime cancer risk of 1.75 in 10,000, which is slightly greater than the 1 in 10,000 upper limit of many regulatory programs' acceptable risk range. Should this upper limit be taken into account in the development of the five consumption advice groups, the HPV would have to be set at the daily intake corresponding to the 1 in 10,000 lifetime cancer risk level, 0.000286 mg/kg/d. The concentration ranges for the five advice groups would be:

Group 1 (No restriction) = 0 - 0.29 mg/kg

Group 2 (1 meal/wk) = 0.30 - 1.24 mg/kg

Group 3 (1 meal/mo) = 1.25 - 5.39 mg/kg

Group 4 (6 meals/yr) = 5.40 - 10.7 mg/kg

Group 5 (No consumption) = >10.7 mg/kg

2.) Appropriate endpoint: Another issue which must be resolved in order to develop the chlordane HPV is what is the most appropriate endpoint to be protected by the HPV. One of the choices relevant to this issue, whether a carcinogenic or noncarcinogenic endpoint is more appropriate, is discussed above. If the issue of cancer risk is to be addressed semi-quantitatively in the advisory, as was done for the PCB advisory, then it is important to choose the noncancer endpoint which is most relevant to human health risks.

The strawman HPV is based on protection against liver damage. However, there are two issues relevant to the strawman HPV which require further deliberation. First, is the USEPA RfD of 0.0005 mg/kg/d truly protective of liver toxicity? Second, is liver toxicity the most relevant endpoint for human health?

Regarding the most appropriate HPV for protection against liver toxicity, the study of Mahon and Oloffs (1979) discussed previously determined a LOAEL for more extensive cirrhotic liver damage in rats pre-treated with carbon tetrachloride at 0.05 mg/kg/d. If this study is used to develop the HPV, the HPV would be 0.00005 mg/kg/d, as calculated in the liver effects section. This would result in the following concentration ranges for the advice groups:

Group 1 (No restriction) = 0 - 0.05 mg/kg

Group 2 (1 meal/wk) = 0.06 - 0.22 mg/kg

Group 3 (1 meal/mo) = 0.23 - 0.94 mg/kg

Group 4 (6 meals/yr) = 0.95 - 1.88 mg/kg

Group 5 (No consumption) = >1.89 mg/kg

It should be noted that this study was not considered by USEPA in the RfD revision, possibly because of some weakness in the study (especially the unexplained absence of compensatory liver hypertrophy usually seen in the early stages of cirrhosis and stimulation of growth in body weight after the carbon tetrachloride treatment ceased). However, it should also be noted that there is likely a small incidence of pre-existing liver disease within the angler population, such that the results of this study may be relevant to the development of a HPV for liver protection.

Regarding the question of whether liver toxicity is the most relevant endpoint for human health, USEPA (1998) touches on this issue in the discussion of the confidence in the RfD. While multiple studies in animals have identified the liver as the primary target of chlordane, this

cannot be unequivocally stated for humans. While the human toxicity database contains numerous case studies of acute and shorter term exposure incidents and several epidemiological studies of longer term exposure, the database does not identify the liver as being clearly the most sensitive target in humans. In fact, it is possible that the nervous and immune systems, and maybe even the reproductive/endocrine system, may be equally or more sensitive to chlordane toxicity than the liver. Lacking better human data, USEPA assumes that the RfD will be protective of all endpoints of toxicity.

Whether this assumption is appropriate may be questioned by the results of a study published after USEPA completed its re-evaluation of the chlordane database. Kilburn and Thornton (1995) evaluated neurophysiological and psychological functions of 216 adults exposed to chlordane in an apartment building from 1987 (the date of termite treatment) to 1994. The study found a number of significant differences from controls in both the neurophysiological tests (deficits in balance, reaction time, non-verbal/non-arithmetic intelligence, short-term memory, and trail-making scores) and the psychological tests (changes in mood-state scores). Indoor chlordane exposures were verified analytically, with 85% of surface wipe samples having detectable concentrations (maximum of 13.6 µg/929 cm2) and 8% of air samples exceeding 0.5 µg/m3. While it is difficult to determine average daily exposures from these measurements, if it is assumed for discussion purposes that the air samples are surrogates for cumulative intake, then an estimate of a LOAEL may be 0.5 µg/m3. Using standard assumptions for an adult breathing rate of 20 m3/d and adult body weight of 70 kg, the daily chlordane exposure is:

$$\text{Daily Exposure} = \frac{0.5\ \mu g/m^3 \times 20\ m^3/d}{70\ kg} = 0.143\ \mu g/kg/d$$

It is worth noting that this "LOAEL" for neurotoxicity is less than USEPA's revised RfD of 0.5 µg/kg/d. It should also be noted that of the various candidate HPVs developed above, that for protection of the endocrine system is less than the strawman HPV of 0.0005 mg/kg/d. If the HPV of 0.00016 mg/kg/d for endocrine effects is used as the HPV, the concentration ranges for the advisory groups would be:

Group 1 (No restriction) = 0 - 0.16 mg/kg

Group 2 (1 meal/wk) = 0.17 - 0.70 mg/kg

Group 3 (1 meal/mo) = 0.71 - 3.01 mg/kg

Group 4 (6 meals/yr) = 3.02 - 6.02 mg/kg

Group 5 (No consumption) = >6.03 mg/kg

3.) Modifying Factor: If a noncancer endpoint is to be used as the basis of the HPV, a third issue must be resolved. As discussed above, a MF of 10 has been used to compensate for the overall weakness of the reproductive/developmental toxicity database for chlordane in developing all the candidate HPVs for discussion purposes. However, also as discussed above, USEPA has chosen a MF of 3 for this purpose, without discussion or justification, in spite of the requirement for a MF of 10 by the Food Quality Protection Act unless it is documented that a lesser MF is justified. If a MF of 10 is employed with the key study used to develop the RfD, the RfD (and strawman HPV) would be 0.00015 mg/kg/d instead of 0.0005 mg/kg/d. If this value were the HPV, the concentration ranges for the advisory groups would be:

Group 1 (No restriction) = 0 - 0.15 mg/kg

Group 2 (1 meal/wk) = 0.16 - 0.65 mg/kg

Group 3 (1 meal/mo) = 0.66 - 2.82 mg/kg

Group 4 (6 meals/yr) = 2.83 - 5.62 mg/kg

Group 5 (No consumption) = >5.62 mg/kg

As a final note, it should be pointed out that all of the noncancer options listed above except the USEPA RfD would result in daily chlordane intakes that would not exceed a 1 in 10,000 lifetime cancer risk if the consumption advice is followed. The highest cancer risk would occur when the HPV using a MF of 10 instead of 3 for liver effects is used, 0.00015 mg/kg/d. The lifetime cancer risk using this HPV is:

0.00015 mg/kg/d x 0.35 (mg/kg/d)-1 = 5.2 in 100,000 = 5.2E-5

**RECOMMENDATION**

In order for the Task Force to decide on the HPV for chlordane, critical evaluation of the issues and options presented above and some difficult choices will be required. Toward this end, the issues and options were discussed at a meeting of the Task Force in Hartford, Connecticut on August 14, 1998 (attended by an invited representative from each Great Lakes state), and some tentative choices were made. As a result, a consensus was reached for a recommendation to the full Task Force for a chlordane HPV, as follows:

- Regarding the cancer risk issue, it was determined that the precedent established with the PCB HPV of addressing cancer risks semi-quantitatively should be maintained with the chlordane HPV; i.e., the HPV documentation and public advisory statements should state that if the advisories are followed then the cancer risk should be no greater than 1

in 10,000. In order for this statement to be true, the revised USEPA RfD may not be suitable as the HPV, since the cancer risk equivalent to exposure at the RfD is slightly greater at 1.75 in 10,000.

- Regarding the issue of what is the most appropriate noncancer endpoint for developing the HPV, discussion centered on whether liver effects or one of the other endpoints evaluated above was the most appropriate endpoint. The members noted that the study reporting increased cirrhotic damage was interesting and potentially relevant to people who eat sport fish, and also resulted in the lowest candidate HPV. However, there were also reservations about the quality of the study such that the results were deemed not appropriate for developing the HPV. The members also noted that the candidate HPV based on endocrine system effects and the human "LOAEL" for neurotoxicity discussed above suggested that the revised USEPA RfD may not be protective of all noncancer endpoints, providing further evidence that the RfD may not be suitable as the HPV. When the discussion of this issued ended, it remained unclear what would be the most appropriate noncancer endpoint for development of the HPV.
- Regarding the issue of whether a 3-fold or 10-fold Modifying Factor was most appropriate, the members were somewhat concerned about the lack of federal guidance on such a choice. It was clear that the relative lack of reproductive and developmental toxicity data in general and the lack of any multigenerational animal studies in particular required a Modifying Factor. After discussion, it was still unclear what that Modifying Factor should be.

After some further discussion, it was decided that a recommendation for an HPV should be made to the full Task Force. It was reasoned that application of a Modifying Factor of 10 for the overall weakness and uncertainty of the chlordane data base (including reproductive/developmental, endocrine, nervous system, and liver effects) to the RfD study was the most appropriate way to develop the HPV. The resulting HPV of 0.15 µg/kg/d is less than all candidate HPVs except that for increased cirrhotic damage, and should therefore be protective of all noncancer endpoints. This HPV will also result in a maximum lifetime cancer risk of 5.2 in 100,000, which is in keeping with the semi-quantitative risk language goal of no more than a 1 in 10,000 risk. Finally, it was reasoned that selecting an HPV different from USEPA's RfD may be controversial, but that there is precedent for this since the PCB HPV does not correspond to any of USEPA's PCB RfDs (for Aroclors 1016 and 1254). Thus, an HPV of 0.15 µg/kg/d is recommended.

## SUMMARY

This paper has presented a review of key toxicity data for chlordane and a discussion of various HPVs which may be developed from this database. Three key issues are identified which must be addressed in selecting the most appropriate HPV for human risk advice: whether cancer or noncancer endpoints are to be used for quantifying fish tissue levels for consumption advice; if a noncancer endpoint is used, what is the most relevant endpoint; and what is the most appropriate Modifying Factor to use to account for the weakness in the reproductive/developmental toxicity database. Preliminary choices for resolving these issues and a recommendation for a chlordane HPV have been made by a subgroup of the Task Force. Once these issues are resolved by the full Task Force, it will be appropriate to select a chlordane HPV which will allow for the development of consistent consumption advice for sport fish contaminated with chlordane.

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Table 1. Candidate Health Protection Value (HPV) and Cancer Risk Information for Chlordane

| Target/ Toxicity Endpoint | Adverse Effect | HPV (µg/kg/d) | Reference |
|---|---|---|---|
| Immune System | Decreased Cell-Mediated Immunity | 1.6 | Spyker-Cranmer, et al., 1982 |
| Reproductive/ Developmental Effects | Deficits in Developmental Markers | 1.0 | Al-Hachim and Al-Baker, 1973 |
| Nervous System | Nervous System Symptoms, Histopathological Lesions | 1.21 | Khasawinah and Grutsch, 1989b |
| Endocrine System | Increased Plasma Corticosterone | 0.16 | Spyker-Cranmer, et al., 1982 |
| Liver | Necrosis | | USEPA, 1998 |
| | (Reference Dose, Modifying Factor = 3) | 0.5 | |
| | (HPV, Modifying Factor = 10) | 0.15 | |
| | Increased Cirrhotic Damage After $CCl_4$ Pre-Treatment | 0.05 | Mahon and Oloffs, 1979 |
| Cancer | 1 in 10,000 Excess Risk | 0.286 | USEPA, 1998 |