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May 24, 2005

Branch Chief Mark W. Townsend
High Production Volume Challenge Branch
Risk Assessment Division
United States Environmental Protection Agency
EPA East, Room 6334AA
1200 Pennsylvania Ave., NW. (7403M), Washington DC.

Attn: EPA HPVC Challenge Program

Dear Mr. Townsend:

Enclosed please find the response to comments provided by the EPA and the Environmental Defense Fund on the Data Availability and Screening Level Assessment test plan for TCC, submitted on behalf of the TCC Consortium to the U.S. EPA's High Production Volume Chemical Challenge Program.

The Consortium appreciates EPA's efforts in ensuring a sustainable high production volume chemical assessment program. Thank you for your attention. Please contact me if I you have any questions.

Sincerely,

Hans Sanderson, **PhD**
Director of Environmental Safety
The Soap and Detergent Association
1500 K St. NW., 20005 Washington DC.

cc: Amuel Kennedy

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EPA/EDF

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TRICLOCARBAN ((TCC) CAS# 101-20-2) CHALLENGE SUBMISSION

TCC Consortium Response to EPA and EDF Comments on: Physiochemical Properties, Environmental Fate, Ecological Effects, and Mammalian Toxicity:

Introduction:

The Triclocarban (TCC) Consortium submitted a test plan and robust summaries to EPA for TCC in 2002. EPA and Environmental Defense (EDF) reviewed this submission and provided comments for both the test plan and the robust summaries. The TCC Consortia appreciates the comments. The comments included physical chemical properties, environmental and ecological effects, and human health effects. EPA concluded that adequate health data are available, for the purpose of the HPV Challenge Program, for acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/ developmental toxicity, as well as environmental safety data. A discrete vapor pressure data point was requested, apart from that no further experimental action was required for the test plan. Moreover, EPA and EDF had some specific comments on the robust study summaries, which will be addressed in the following. The TCC Consortia appreciates the comments and share the overall conclusions

Physiochemical Properties. The submitter needs to provide a discrete value for vapor pressure.

The vapor pressure of TCC was quantified following the test procedure Method A4 specified in EU Commission Directive 92/69/EEC (which constitutes Annex V of Council Directive 67/548/EEC) under GLP (according to OECD, 1997, ENV/MC/CHEM(89)17) at ambient temperature (25° C) to be 4.6×10^{-11} Pa using vapor pressure balance (SafePharm Laboratories (SPL) Project Number 2224/0001 (2006)).

$$\text{TCC vapor pressure} = \underline{4.6 \times 10^{-11} \text{ Pa}}$$

Environmental Fate. The data provided by the submitter for photodegradation, stability in water, and fugacity are adequate for the purposes of the HPV Challenge Program. The submitter needs to clarify biodegradation and fugacity results and address some deficiencies in the robust summaries.

Biodegradation: Submitters agree ready biodegradability can not be determined from adapted sludge test. Ready biodegradability assays are of limited use for biocides because at the test concentrations in these assays they have a deleterious effect on the microbial community in the test. However the existing data show clearly that at realistic concentrations triclocarban undergoes rapid primary biodegradation (half-life = 0.12

hrs.) in activated sludge followed by ultimate degradation of intermediate degradation products.

As stated in section 2.3.1 of the HPV "Test plan" document, even though TCC is not readily biodegradable, TCC biodegrades in adapted activated sludge, with 100% loss of the parent compound and 50% mineralization rate (Gledhill, 1975, Water Res 9: 649).

While no biodegradation was observed in an OECD 301C ready biodegradation test, given the concentration of TCC in the test (100 mg/L) and its biocidal nature, it is likely that TCC killed the inoculum. In Gledhill's (1975) work, TCC radiolabeled in the *p*-chloroaniline ring (¹⁴C-PCA-TCC) was extensively mineralized to ¹⁴CO₂ in batch studies with raw sewage and activated sludge. While TCC, radiolabeled in the 3,4 dichloroaniline ring (¹⁴C-DCA-TCC) exhibited less mineralization, the level of mineralization increased in the presence of co-substrates. Hence, batch studies indicated, that TCC underwent rapid primary biodegradation but metabolites derived from the dichloroaniline moiety mineralized more slowly by co-metabolism.

Consequently, realistic continuous activated sludge (CAS) studies were conducted to more accurately assess fate of TCC under actual sewage treatment conditions. In a CAS study with ¹⁴C-PCA-TCC, only 3.2% of the radioactivity dosed into the **influent** remained in the effluent at steady state. Approximately 1.2% of the dosed material was found in the effluent as intact parent, while < 0.05% was in the form of *p*-chloroaniline. In a concurrent CAS study with ¹⁴C-DCA-TCC, 30.3% of the radioactivity dosed into the **influent** was present in the effluent. Approximately 2% of the dose was present in the effluent as intact parent and 2.2% was present as dichlorophenol. Hence removal of parent TCC was 98% or greater as a result of sorption, mineralization and biodegradation to more polar metabolites.

In addition, monitoring studies to measure TCC removal in municipal trickling filter and activated sludge wastewater treatment plants in the US and UK (Table 2.4 of the submitted TCC HPV report) show that on average 94% of TCC is removed in operating activated sludge wastewater treatment plants. This removal is consistent with the removals measured in the CAS laboratory tests of 98%.

Removal data from a CAS study or activated sludge treatment plant can be used to estimate a biodegradation rate and half-life for a chemical. The equations describing the level of a chemical in effluent are:

$$C_{diss} = \frac{C_{inf}}{1/SRT + k_1HRT} \quad (1)$$

$$C_{sorb} = C_{diss}K_dS_{eff} \quad (2)$$

$$C_{eff} = C_{diss} + C_{sorb} \quad (3)$$

C_{diss} = the concentration dissolved in the effluent (mg/L)

C_{inf} = the concentration in the

K_d = sorption coefficient (U/kg)
SS_{reac} = the suspended solids concentration in the reactor
HRT = the hydraulic residence time (hrs)
SRT = the solids retention time (hrs)
k₁ = the first order biodegradation rate (hrs⁻¹)
C_{sorb} = the concentration sorbed to solids in the effluent (mg/L)
SS_{eff} = the suspended solids concentration in the effluent
C_{eff} = the total concentration in the effluent (mg/L)

Using these equations, the first order biodegradation rate (k₁) can be back calculated from the 98% TCC removal in the CAS study. The reported HRT was 10 hours and a sorption constant (K_d) of 19,000 L/kg can be estimated from CAS data. The other variables can be assumed to be equal to typical values encountered in standard treatment processes: SS_{reac} = 0.0025 kg/L, SRT=240 hrs and SS_{eff} = 0.00001 kg/L. Based upon these inputs, the calculated biodegradation rate is 5.6 hr⁻¹. This value translates into a half-life of 0.12 hrs in an activated sludge system. Given this short half-life in a sewage treatment plant, the half-life of any remaining TCC and its metabolites in other habitats is likely to be relatively short, since the same microorganisms that degrade TCC and mineralize its metabolites in the treatment plant will be released in the effluent, continue to degrade TCC in surface waters, and colonize sediments downstream from sewage treatment plants.

Fugacity: The data in the original submission were correct. Fugacity simulation Level III v 2.2 yields 70% in the water and 29% in the sediment. Some confusion may have resulted because this is an assessment of the post-treatment TCC. Clearly, the vast majority of TCC in wastewater is associated with solids, and is removed from the wastewater stream with the solids. Some undergoes primary and subsequent biodegradation during treatment. The remainder, leaving the wastewater treatment plant with the effluent is reapportioned in the receiving streams between the water and sediment. This fugacity estimate is that 70% of this material is in the water.

Ecological Effects. Data for acute fish, daphnids, and algae in addition to the 21-day chronic toxicity study are tentatively acceptable pending receipt of adequate/enhanced robust summaries.

Additional Details of Reported Studies:

EPA comments indicated additional data from reported studies would be helpful to fully assess their adequacy. These additional details are summarized below to the extent they were available in the study reports:

Acute Invertebrate Toxicity (*Ceriodaphnia dubia*). Robust Summary p. 19 Reference # 31

Type	:	Static
Test group number	:	32 (4/concentration)
Test group size	:	20/concentration
Statistical Methods	:	Nonlinear interpolation (Probit)
Test concentrations (nom.)	:	(µg/L) 25, 15, 9, 5.5, 3.3, 1.3, 0 (control) and 0 (solvent control)

Test concentrations (anal.) : (µg/L) 17, 11, 6.3, 3.8, 1.9, 0.69, 0, 0
 Control response : 0 mortality
 96hr 0 mortality : 5 µg/L

Acute Invertebrate Toxicity (*Daphnia magna*).

Robust Summary p. 19 Reference # 30

Type : Static
 Test group number : 30 (3/concentration)
 Test group size : 15/concentration
 Statistical Methods : Probit analysis, binomial probability, moving average angle analysis
 Test concentrations (nom.) : (control), and 0 (solvent control)
 Control response : 0 mortality
 46 hr. 0 mortality **conc.** : 9.2 µg/L

Acute Invertebrate Toxicity

Robust Summary p. 20 Reference # 32

Type : Flow Through
 Test group number : 24 @/concentration), at each of 7 sediment concentrations.
 Test group size : 1 0/concentration
 Statistical Methods : Probit analysis, binomial probability, moving average angle analysis
 Test concentrations (nom.) : (control), and 0 (solvent control)
 Control response : 0 mortality
 96hr 0 mortality : 5 µg/L

Chronic Invertebrate Toxicity (*Daphnia magna*).

Robust Summary p. 24 Reference # 39

Type : Flow Through
 Test group number : 28 (4/concentration)
 Test group size : 10/concentration
 Effects measured : % survival, mean length, weight, reproduction (days to first brood and young/adult)
 Statistical Methods : One-way ANOVA, student T-test, Fischer's exact (one-tailed) with Hochberg adjustment
 Test concentrations (mea.) : (µg/L) 1.0, 1.1, 2.9, 4.7, 8.5, 0 (vehicle control)
 Control response : 2% mortality

Endpoint	Survival	Days to first brood	young/adult/day	length	weight
21day NOEC	4.7	4.7	4.7	2.9	4.7
21day LOEC	6.5	8.5	8.5	4.7	8.5
14-day EC-1 0	4.6		4.7		
EC-20	4.9		4.6		
EC-S0	6.0		5.6		
21day EC-10	4.8		4.2		
EC-20	5.0		4.7		
EC-50	5.3		5.6		

Chronic Invertebrate Toxicity (*Ceriodaphnia dubia*).

Robust Summary p. 24 Reference # 41

Type : Static Renewal
 Test group number : 7
 Test group size : 1 0/concentration

Effects measured : % survival, reproduction (young/adult and days to first brood)
 Statistical Methods : One-way **ANOVA**, Fischer's exact (one-tailed) with Hochberg adjustment
 Test concentrations (nom.) : (**µg/L**) 1.9, 3.8, 7.5, 15, 30, 0, 0 (vehicle control)
 Test **Conc.** (mean measured): (**µg/L**) 0.22, 0.41, 0.75, 1.46, 2.48 0, 0 (vehicle control)
 Control response : 10% mortality
 Solvent control response : 0% mortality

Concentration (µg/L)	Survival	Days to first brood	young/adult/day
0	90	4.1	5.4
0 (vehicle cont.)	100	4.0	6.3
0.22	100	4.0	5.4
0.41	80	4.0	4.7
0.75	90	4.0	5.1
1.46	90	4.1	4.8
2.84	90	4.0	3.8

Chronic Invertebrate Toxicity (***Mysidopsis bahia***). Robust Summary p. 25 Reference # 43

Type : Flow through
 Test group number : 7
 Test group size : **20/concentration**,
 Effects measured : mortality, time to brood pouch formation, #offspring, offspring mortality
 Statistical Methods : One-way **ANOVA**, **Dunnett's** procedure
 Test concentrations (nom.) : (**µg/L**) 0.06, 0.12, 0.25, 0.50, 1.0, 0, 0 (vehicle control)
 Control response : mortality
 Solvent control response : 15% mortality

Concentration (µg/L)	28day mortality%	Offspring/hatch
0	15	7.5
0 (vehicle cont.)	5	7.0
0.06	15	6.6
0.12	30	4.0
0.25	85	0
0.5	100	
1.0	100	

Chronic Invertebrate Toxicity (***Daphnia magna***). Robust Summary p. 25 Reference # 44

Type : Flow Through
 Test group number : **32 (4/concentration)**
 Test group size : **20/concentration**
 Statistical Methods : % survival ■ moving angle with analysis of variance, and instantaneous pop growth.
 Test concentrations (nom.) : (**µg/L**) (vehicle control)
 Control response : 0 mortality
 % survival and inst. reproductive rate (r) :

Day	7	14	21	r
Conc. (µg/L)				
0 (Control)	100	89	70	0.36
0.062	100	96	82	0.38
0.12	100	96	76	0.38
0.25	95	90	58	0.36

0.5	0	0	0	-
1.0	0	0	0	

Chronic Invertebrate Toxicity (*Daphnia magna*), in the presence of suspended sediments and secondary sewage treatment solids. Robust Summary p. 26

Reference # 45

Type Flow Through
 Test group number 28 (4/concentration)
 Test group size 20/concentration
 Statistical Methods : % survival and reproduction
 Test concentrations (nom.) : (µg/L) 1.9, 3.8, 7.5, 15, 30, 0, 0 (vehicle control)
 Suspended sediment **conc.:** 50 mg/l.
 Sewage Effluent **conc.:** 10%
 % survival and (cum young/female):

Day:	7	14	21	28
0 (Control)	99(0)	95(71)	94(152)	85(252)
0 (vehicle cont.)	99(2)	96(82)	94(150)	80(240)
1.9	99(1)	99(70)	94(144)	88(236)
3.8	100(2)	95(73)	92(144)	88(256)
7.5	95(0)	94(72)	90(135)	85(258)
15	0	0	0	0
30	0	0	0	0

Environmental Defense Fund Comments:

The chronic PNEC for TCC was estimated to be 0.15 µg/L. Environmental monitoring data shows Delaware River surface water concentrations of 0.2 µg/L. Hence, every effort should be made to reduce TCC concentrations.

We believe the TCC PNEC derived in the HPV document is conservative and protective of the environment. Typically, a factor of 50 is applied to the lowest chronic toxicity value when two chronic NOEC/EC_x values are available. When three chronic NOEC/EC_x values are available, a factor of 10 is used on the lowest. When 10-15 chronic NOEC/EC_x values are available, a distributional approach is commonly used and concentration predicted to be lower than 95% of the chronic toxicity values is estimated (referred to as the HC_{5,50}). For TCC, there are 7 chronic toxicity values. Using the distributional approach, we estimate the HC_{5,50} is 0.6 µg/L. This further suggests the factor of 10 is conservative and a more appropriate PNEC would be approximately 0.6 µg/L.

Furthermore, 0.2 µg/L is neither typical of river water concentrations, nor likely to be in a soluble and available form. River water samples were collected and analyzed in 1985-1987. While TCC usage has remained constant since that time, wastewater treatment technology has progressed. The number of trickling filter plants has declined and the percentage of wastewater treated by highly efficient activated sludge wastewater treatment systems has increased. Hence, the current TCC HPV document states that "Many of the locations sampled during this period did not have advanced

wastewater treatment in place. Improved wastewater treatment systems in these areas would likely improve TCC removal in wastewater and result in decreased levels of TCC in WWTP effluents. Based on the results from the monitoring studies in 1979, 1982, 1985 and 1987, the TCC concentration of 0.05 µg/L should be regarded as a high-end predicted concentration in surface waters (PEC).” Further, aquatic toxicity studies are performed with well water containing low levels of organic carbon and suspended solids. Hence, most or all of the TCC in a toxicity study is available for uptake and toxicity. In the environment, however, organic carbon and suspended solids sorb materials and make them unavailable for uptake and toxicity. In a recent study, Halden & Paull (2005, *Environ. Sci. Technol* **39**:1420) report that 72% of the total triclocarban is sorbed onto particulates (the TCC concentrations they measured were impacted by up to 99% raw sewage from illegal discharges (Sanderson, 2005, *Environ. Sci. Technol* **39**:6334) and are thus not representative of PEC (Halden & Paull, 2005, *Environ. Sci. Technol* **39**:6335). They did not account for the amount sorbed onto organic carbon. Hence, the amount of TCC in the environment which is available for uptake and toxicity is 28% or less of the total measured amount. More recent studies presented at FDA-NDAC Oct. 2005 by Dr. Halden suggest that the average PEC = 0.0084 µg/L (unpublished data), which is still significantly below the PNEC = 0.6 µg/L.

Data reported on pages 24 and 25 of the robust summary seem to report that the NOEC is much lower in chronic toxicity studies on aquatic invertebrates. For example, a NOEC of 0.06 is reproductive effects in Mysidopsis bahia and similar results are reported for other reproductive studies on aquatic invertebrates. If these data are correct, then current surface water concentrations of TCC are clearly too high and should be decreased.

The data on mysids is correct. However, it is unclear what is meant by the sentence: “similar results are reported for other reproductive studies on aquatic invertebrates”. Mysids are marine organisms, exposure concentrations in the marine environment are likely much lower due to higher dilution. The toxicity data on the mysids are far below that of other organisms suggesting that toxicity for marine organisms may be greater than for freshwater organisms. Due to the physiological differences and potential differences in the availability of TCC from saltwaters, the mysid value is inappropriate to use in the freshwater PNEC.

Mammalian Toxicology

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/ developmental toxicity)

Acute Toxicity

EPA concluded that the data submitted for acute toxicity, conducted under EEC guidelines, was acceptable. No additional information was requested for this end point.

Repeated-Dose Toxicity

Comment 1

For repeated-dose toxicity, EPA requested that the dossier state if clinical chemistry and hematological parameters were evaluated in the 30-day study.

Response 1

A review of the original report (Monsanto 1960, Younger Laboratories Project # Y-60-39) found no evidence that clinical chemistry and hematological parameters were evaluated in this study.

Comment 2

EPA requested that the organs examined in the 24-month study be listed and a full reference be supplied, including the date of publication.

Response 2

The 24-month study examined different tissues for each dose group. The tissues examined for the low (25 mg/kg/day) and mid (75 mg/kg/day) dose groups included the testes/epididymides, liver, kidney, spleen, bone marrow, and mesenteric lymph nodes, as well as tissue masses and gross lesions. The selection of tissues to be examined for the control and high-dose group (250 mg/kg/day) was based on a comprehensive gross postmortem examination (killed at scheduled sacrifice, killed *in extremis*, or found dead). A whole list of tissues was available (preserved) for examination and included adrenal glands, bone marrow (sternal), brain, eyes, epididymides, gonads (ovaries and testes), heart, intestines, kidneys, liver, lungs, lymph node, mammary gland, sciatic nerve, pancreas, pituitary gland, salivary glands, seminal vesicles, skeletal muscle (biceps femoris), skin (right inguinal), spinal cord (cervical), spleen, stomach, thymus, trachea, thyroids/parathyroids, urinary bladder, uterus/prostate, gross lesions, tissue masses or suspected tumors and regional lymph nodes.

The full reference for this study is "A 24-Month Dietary Toxicity/Carcinogenicity Study of TCC in Rats", Monsanto 1981, Bio/dynamics Project # 77-I 785, BDN-77-280.

Reproductive Toxicity

Comment 3

Regarding reproductive toxicity, EPA concluded that the robust study summary for a three-generation feeding bioassay in rats omitted details, including the reproductive organs examined and whether implantation sites were recorded.

Response 3

A review of the original report (Monsanto 1983, Bio/dynamics Project # 79-2398, BD-79-058) indicates that the primary reproductive organs (gonads), the testes in the male and

the ovaries in the female, were examined from all parents (F₀, F_{1b}, F_{2b}) and from the same 100 F_{3b} weanlings. These tissues were also examined from all other animals if they were grossly abnormal. There is no evidence in this report that implantation sites were recorded during this study.

Environmental Defense Fund

The Environmental Defense Fund (EDF) also reviewed the robust summary and test plan for Triclocarban. The EDF agreed with the submitter that data is sufficient to fulfill requirements of the HPV program and that no new studies are needed. The EDF had two specific comments related to health effects. These comments are addressed below.

Comment 4

EDF confirmed TCC's safety based on the mammalian toxicity data. TCC has low acute toxicity, is negative in genetic toxicity tests and is also negative for carcinogenesis in a 2-year bioassay in rats. The EDF also agreed that there are few or no apparent effects observed in the well-conducted reproductive and developmental toxicity studies that were performed.

Response 4

The TCC Consortium agrees with this observation from EDF.

Comment 5

EDF commented on the NOAEL value of 1000 mg/kg bw/day originating from the 30-day repeated dose study in Table 3.1, and its apparent conflict with a NOAEL value of 25 mg/kg bw/day in a 24-month cancer study also reported.

Response 5

The TCC Consortium agrees with this observation from EDF. The cancer study reports significant changes at the mid dose of 75 mg/kg bw/day. Therefore, the NOAEL value should be adjusted to 25 mg/kg bw/day. The 25 mg/kg bw/day was used for the consumer risk characterization resulting in margin of exposure (MoE) ranging from 4,167 to 18,115,942 (Table 3.4 of the test plan).

On Behalf of the TCC Consortia;

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