Appendix 1

Amending the Docket: Corrections to Misstatements on Triclosan made during the 20 October NDAC Panel Meeting

Below is a list of editorial and scientific corrections to statements made during the panel meeting regarding triclosan.

Excerpts from the official NDAC meeting transcripts and speaker's slides:

This detailed commentary is related only to the antiseptic TRICLOSAN mentioned in the transcripts and slides. The numbering of the comments is: transcript page, line number; or respective slide number. Bracketed comments clarify the issue if not perceivable from the quotes.

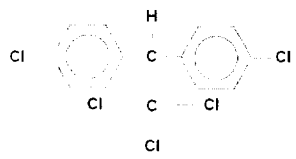
Secondary Routes of Exposure, Rolf Halden PhD, PE

1. **Transcript page 95, line 6:**

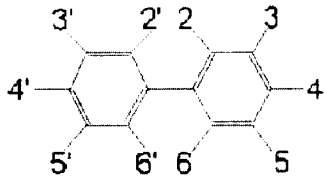
They come from the haydays of pesticides. We had DDT. We made PCB...(Triclosan is similar to all other chlorinated aromatics)

Incorrect statement/ Inaccuracy

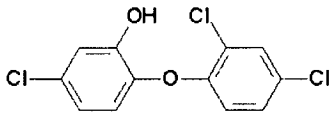
Triclosan is a chlorinated biphenyl-ether and not used as an agricultural pesticide.



DDT



PCB



Triclosan

(numbers = possible chlorine substituents)

The comparison of triclosan to both DDT (dichlorodiphenyltrichloroethane) or PCB (polychlorinated biphenyls with 1-10 chlorine substituents) is completely misleading from structural and substituent properties as well as from toxicological and environmental behaviour.

The half-life of DDT is ~10-20 years in nature and about 1 year in humans, while triclosan is shown to degrade easily in natural waters and soils and has a rapid pharmacokinetic profile in humans. DDT was directly applied to ecosystems widely in large quantities while triclosan has not. The NOEL of DDT is 0.184 mg/kg body weight and triclosan has a NOEL of 50 mg/kg body weight. DDT builds up in the food chain and accumulated while triclosan does not show this phenomenon due to its degradability.

The higher chlorinated PCB have been known and used for their non-reactivity and are, hence, of superior longevity. They therefore build up in food chains if not disposed of properly and find entry into natural systems. They have never been used as pesticides or as antimicrobials.

2. Transcript page 95, line 22:
...and they really like fat, and unfortunately, we are fat . . . they will leave the water and come to us and stay with us (accumulation of Triclosan in fat and fatty tissues)

Incorrect statement/ Inaccuracy

Triclosan does not accumulate in fat or fatty tissues. It may enter the body orally through the use of toothpaste or dermally via cosmetics. It is rapidly metabolized in the liver (first-pass effect) to form mainly glucuronide and other conjugates. Triclosan and its metabolites are excreted in the urine with resident biological half-lives of < 30 hours (data from toothpaste studies). The possible occurrence of triclosan in breast milk has no link to accumulation in fat (in contrast to environmentally persistent substances) as evidenced by the pharmacokinetic data on triclosan.

An occurrence in breast milk samples may be due to the use of e.g. triclosan-containing toothpaste or other personal care products, with resulting bloodstream levels and secretion via the lactiferous gland. Presence may also be an artifact of sample collection, such as body cleansing with an antibacterial body wash prior to expression in which surface residues entered the sample or container washing with antibacterial soaps. Uptake from environmental sources can be safely excluded.

The levels of triclosan reported in breast milk samples is more than 1000 times lower than levels proven safe for human intake. Therefore, the concentrations of triclosan reported in breast milk do not harm either mothers or breast-fed infants.

3. Transcript page 97, line 5:
... it can form 2-chlorodibenzoparadioxin. (Triclosan is a precursor of Dioxins: 2,8-DDD; 2,4,7,8-TCDD)

There is evidence that triclosan can be photo-degraded to 2,8 dichlorodibenzodioxin, one of the non-toxic compounds of the family. The 2,8 DDP is instable itself and will be further degraded rapidly. A transformation to toxic dioxins has never been shown and is highly unlikely since chemical chlorinations would have to take place. Any impurities present due to production processes are

cleaned from triclosan and responsibly disposed in Ciba's production facilities to much below the level regulated by the US-Pharmacopeia.

4. Transcript page 97, line 8:
Triclosan is persistent because it is a chlorinated aromatic (environmental persistence of all chlorinated aromatics are similar)

Incorrect statement/ Inaccuracy

Many studies indicate that triclosan is readily degradable in waste water treatment and surface waterways (Federle et al. 2002, Sabaliunas et al. 2003, McAvoy et al. 2002, Morall et al. 2004). Wastewater treatment plants systematically reduce the incoming triclosan load. Many assessments mentioned before show a range of 70- >95% depending on the treatment technology with most plants being >90%. This means of every 100 grams triclosan flowing into a well working plant 95 grams are biodegraded while 3 gram adsorb to sludge and 2 grams remain in the outflow. Federle et al. (2002) clearly showed that >90% of radioactive activity in their experiments with radio-labelled triclosan was found in the gas phase as carbon dioxide and hence produces by biodegradation (>95%). Sorption played a much minor role (5%).

Unpublished reports from the same author show that biodegradation is going on at a high rate in natural surface waters and in raw sewage die away studies (Schwab and Federle, Federle and Schwab, unpublished, see appendix). Sabaliunas et al. (2003) showed for an intensively monitored watershed in the UK (GREAT-ER modelling project) that the half-life of triclosan in surface streams was 2.1- 3.3 hours and faster than BOD-removal (organic matter). Morall et al. (2004) were able to show that 76% of the triclosan entering a stream via waste water outflow was removed by degradation and in a smaller fraction (14.3%) by sorption within a few miles of water travel. Sorbed triclosan will be degraded in the normal breakdown processes of organic matter once the sorbent is degraded. Settling plays a minor role in streams where deposits are frequently agitated via turbulence in high water situations.

Studies for soil degradation show that triclosan half-lives in soils are in the range of days (see study 25 summaries in appendix); and that there is no accumulation in soils.

5. Transcript page 97, line 9:
... because it is a chlorinated aromatic (All aromatic and chlorinated compounds behave similar)

Incorrect statement/ Inaccuracy

The chlorination of a compound is not generally resulting in the similar behaviour of the substances. Chlorination if often used to stabilize manmade chemicals or to add active moieties like in many pharmaceuticals. Chlorination is not the characteristic of a chemical trouble maker as was insinuated in the comments made.

6. Transcript page 97, line 14:
Chlorinated aromatics do bio-accumulate ... and Triclosan is not an exception here ... this chemical has been detected in fish

Triclosan does not bio-accumulate in food-chains because it is conjugated and excreted by animals and man by their metabolism. If a constant inflow occurs a steady concentration will be present in body fluids. These steady state concentrations can not be interpreted as accumulation and there is no triclosan remaining some time after cessation of intake. For zebra fish this clearance time was measured to be around 5 days when exposed in water containing 35-59 µg/L triclosan after 5 days plateauing to steady state concentrations. [26]

Triclosan has been detected in fish bile (Adolfsson-Erici et al. 2000) from animals exposed to sewage treatment outflows or river sediment. Uptake mechanism in both cases was from feeding on organic particles. The risk assessment for the aquatic and terrestrial compartment including fish-eating birds clearly showed no concern for these exposure routes.

7. Transcript page 97, line 19:
There is speculation that triclosan might function as an endocrine disruptor. There is really no firm data on this.

Research to date has not been able to validate the hypothesis that triclosan may function as an endocrine disruptor.

As of December 2005, the Endocrine Disruptor Methods Validation Advisory Committee form at the request of the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), a federal advisory committee formed in 1996 to make recommendations to EPA on how to develop a scientifically defensible screening program that would provide EPA the necessary information to make regulatory decisions about the endocrine effects of chemicals, has not finalized the testing method for any of the 17 proposed screening assays. Based on this it is difficult to evaluate the relevance of data in the published literature.

[26] Schettgen et al. 1999

8. Transcript page 97, line 24:
Carcinogenicity, mutagenicity, teratogenicity ... the chemical itself probably is not ... but possibly, you know, some of the impurities, for example, dioxin

Incorrect statement/ Inaccuracy

Clinical studies clearly demonstrate that triclosan is neither carcinogenic or mutagenic, nor teratogenic. So there is no probability left that it could be. In respect to impurities mentioned it is obvious that the consumer will not come in contact with these (if product is proper USP grade) so the argument seems to be a scare and a reason to mention dioxin once more.

9. Transcript page 99, line 13:
... since there is no information on environmental fate of these chemicals we did some quantitative structure, activity relationship analysis suggesting that the half-life of both substances ... is two months in water and fairly long in soil and particularly in sediment

Incorrect statement/ Inaccuracy

In slide 5 the speaker showed the amount of literature available for triclosan, therefore it is unclear why structure-activity relationship analysis was used in place of existing real-world data.

There are real-world half-life and degradation data available for aquatic, terrestrial and biotic compartments and the environmental fate including published risk assessments available on the compound (Reiss et al. 2002). Half-life in the water column of natural streams has been shown to be significantly shorter and in the range of hours (Morall et al 2004; Sabaliunas et al. 2002, Federle et al. 2002). The half-life in soils is in the range of days depending on organic matter and water content and on availability of oxygen. The half-life in sediment will depend on the same parameters. Several reviews have been done by authorities or are ongoing neither of which has led to a negative opinion.

10. Presentation slide 9:

The speaker insinuates with the headline of this slide that the estimated half-lives are indicative of the persistence of triclosan. It is clearly unjustified to attribute a substance with half-life of days and weeks in nature persistent. Triclosan degrades in the aquatic environment as fast as other organic matter and is degraded in soils in days.

It is surprising that the speaker estimates these values. These estimated values are clearly much higher than others having been measured and reported in the reviewed literature.

11. Transcript page 100, line 9:
... for personal care products we study whether they are adsorbed through the skin (Lack of data on personal care consumer products);, . ..other routes of exposure than the one we intend

Incorrect statement/ Inaccuracy

There is a huge amount of studies and published data available to document the intake, pharmacokinetics, toxicology, and excretion of triclosan in humans. There are very solid teratogenic studies available which have been submitted to the FDA. For triclosan it is evident, that an oral intake will take place and it is safe to be used as an oral care ingredient.

The firm statement that other routes of exposure apart from the intended uses exist is misleading and the speaker fails to prove this speculation. The conclusion that the loop to secondary exposure through agricultural crops or animals to humans is closed is a misleading statement given the mass flow in the environment.

The speaker insinuates that excretion of triclosan is a result of unwanted intake through a secondary route, such as contaminated drinking water or crops. Any excretion in urine, presence in breast milk and blood is a result of the deliberate intake or absorption from product use. Studies and risk assessments show that it is without risk to humans.

12. Presentation slides 11-12:

The slides 11-12 insinuate that a significant secondary route of exposure exists, however, quantitative considerations and mass balancing have not been presented by the speaker. Mass balancing from data collected and published (e.g. McAvoy et al. 2002) shows that any secondary route of exposure will be insignificant in relation to primary routes of exposure.

Incorrect statement/ Inaccuracy

The bold typed routes of exposure, absorption for personal care products (slide 11) and ingestion from secondary exposure (slide 12) are incorrect and misleading. For triclosan, the major route of exposure is oral ingestion of oral care products and to a lesser extent, absorption of triclosan from soaps, washes and de-

odorants. All these applications are safe and have a large margin of safety even when used in combination in a maximum use scenario.

The speaker fails to quantify the secondary exposure route of ingestion, and the argument that excretion in urine is a proof for secondary exposure is completely inaccurate.

13. Transcript page 100, line 16:
... other routes of exposure other than the one that was intend(ed).

Unsubstantiated statement/ Inaccuracy

Proper mass balancing of the pathways of triclosan from the use of consumer products, inflow into WWTP, outflow of water and removed sludge clearly shows that the speculation the speaker lays out is not valid. Based on the measurements of McAvoy et al. (2002) for US WWTPs and sludge removal and application rates from US EPA databases the following mass balance demonstrates the improbability:

Annual sludge generation in US sewage plants is believed to be 5.4 million dry metric tons. Of these, 21.9% (1.2 mio mt) are applied to agricultural land including grazing land. Average sludge application rates are considered to be 1.35 kg/m^2 (EPA National Sewage Sludge and Needs Survey, 1988, EPA Biosolids Technology Factsheet, EPA 832-F-00-064).

For the total US, multiplying 1.2 mio mt sludge with 4.2 mg/kg triclosan in Loveland-plant type sludge gives 5040 kg/year triclosan that can potentially be put on agricultural land in the US through biosolids application. For the least effective Glendale-plant a total of 18700 kg/year can be calculated. Average removal efficacy in US plants, however, are much higher than in the Glendale plant, hence, the reality will be between both values (all data and plant names from McAvoy et al 2002).

Further assuming average sludge application rates of 1.35 kg/m^2 on agricultural land the applied total mass of triclosan would be 1.21 mg/m^2 for a Columbus-plant type sludge, 5.67 mg/m^2 for Loveland-plant type sludge and 21.06 mg/m^2 for the least effective trickling filter plant sludge (Glendale-plant). As a quick reality check, we calculated the toxicological impacts: Ingesting 1.35 kg of the respective sludge applied to one square meter would result in an uptake similar to brushing the teeth 0.3 - 5.6 times with triclosan containing toothpaste (1.25 g toothpaste per brushing, 0.3% triclosan, 3.75 mg triclosan, swallow dental slurry). Sludge will be worked into around 20 cm of soil and therefore diluted by a factor of 300 (weight/weight).

It remains unclear from the statements of the speaker how this could result in any risk for man. Additionally there are rapid removal mechanisms at work ensuring that the remaining triclosan will be removed from soil within days *(soil studies, see study summaries in appendix).*

14. Slides 14-23:
Co-occurrence with TCC, modelling

The speaker has obviously specialized in Triclocarbanilid detection, modelling and predictions. It remains unclear, however, how these detections and model runs translate into solid numbers and peculiarly into risk assessments of the ecological compartments and biota at large.

15. Transcript page 105, line 20:
Therefore what we see in the USGS data are kind of worst-case scenarios

This statement is agreeable and it has been shown in industry's presentation that there is no permanent negative effect from these values of concentration neither to aquatic organisms due to the prevailing NOELs.

16. Transcript page 107, line 17; Related presentation slides 27, 28:
We took an unusual approach of doing a mass balance

Incorrect statement and conclusions

What is shown in these slides are clearly **no mass balances** but comparisons of concentrations (parts per billions) being a relative measurement. The speaker fails to relate these to flow data for water or actual mass data for sludge. Much more water mass runs through a wastewater treatment plant than sludge is generated for which a rule of thumb rate is: **1 kg sludge is generated from 10000 L (and greater) of water treated.** The differences in concentration can therefore not be attributed to accumulation and the calculation must not be called mass balance.

In the following table measured values from McAvoy et al. 2002 for activated sewage sludge plants are calculated into a mass balance using official EPA sludge generation data.

Table 1. Triclosan concentrations and masses in inflow, sludge and outflow, sludge concentrations and quantities and combined triclosan outflow

plant	Inflow TCS conc µg/L	Out-flowTCS conc µg/L	Inflow TCS gram/d	Out-flowTCS gram/d	Outflow TCS % of inflow	Sludge TCS conc mg/kg	Sludge mass (calc *) kg/d	Sludge TCS content gram/d	TCS sludge out % inflow	TCS combined outflow % inflow
[redacted]	5.41	0.24	1630	51.2	3.14	0.9	22898	20.6	1.26	4.4
[redacted]	10.7	0.41	110	5.0	4.5	4.2	690	2.89	2.62	7.12

(*) calculated on the basis of 47 lbs (21 kg) dry matter annually per capita serviced (from EPA biosolids factsheet)

It is obvious when taking flow and mass figures into account that a real mass balance looks much different from what was shown in the speaker's slides. From table 1 it becomes clear that in well working activated sludge plants, the combined TCS elimination is >90% and sludge contains even less triclosan mass than the water due to the quantitative relationship.

In his slides, the speaker seemed to pick the highest values from McAvoy et al 2002 for digested trickling filter plant sludge (15.6 mg/kg triclosan; sludge volume reduced by > 50% in comparison to undigested, the values would be 7.50 mg/kg) from a single small and not state-of-the-art trickling filter plant, neither naming the source of data nor giving average or range. Overall, US WWTP show much higher effectiveness.

17. Transcript page 108, line 18 and Presentation slide 29:
The red piece of the pie is the fraction that we believe is not degraded (slide 29).

The percentages shown in the slide cannot be derived from any of the previous slides or any other source and it is marked on the slide that the percentages are estimates. However, these estimates, again, differ considerably from peer reviewed data in the literature, even considerably from the highest numbers available (Singer et al. 2002; McAvoy et al 2002; Bester 2003). Based on the literature, it is scientifically incorrect to state that "the plants, they remove, but do not degrade the chemicals", since exactly this has been shown to occur in many reviews.

18. Transcript page 111, line 14:
We did another prediction. Again we predicted first we have these chemicals across the United States....From the plant, we calculated the average usage of mass per person, extrapolated to the United States, and made a crude estimate and this is just what it is, a crude estimate...We estimated

that 150,000 pounds of triclosan ... are applied every year in sludge on agricultural fields used for either grazing or crop production.

Miscalculation, Incorrect statement and conclusion

In their recent publication, Halden and Paul 2005 (page 1423) assume a total triclosan consumption of 330 metric tons per year for the USA.
In his presentation the speaker estimated 150.000 lbs (= 68 mt) triclosan being applied to agricultural soils. The speaker fails to match these numbers consistently. In slide 29 he speaks of 43% of all triclosan used being on sludge and (on slide 31) 63% to be land applied. This adds up to 90 mt. In addition, the speaker fails to name the source for the calculations.

In contrast to data given in **slide 31**, of the (5.4 million metric tons) sludge annually generated in US waste water treatment plants only 21.9% are brought to agricultural or grazing land. The data shown in the slide for land application gives information on all land applications, which encompasses forests, reclamation sites, landscaping, parks, golf courses, lawns and gardens. Additionally, on page 1 of the cited publication ("Biosolids applied to land", Natl Res Council of the Natl Acad 2002; http://www.epa.gov/waterscience/biosolids/nas/complete.pdf) it is stated: EPA estimates that sewage sludge is applied to approximately 0.1% of the available agricultural land in the United States on an annual basis.

According to EPA's National Sewage Sludge Survey (1988), 16.1% of the sludge is incinerated, 34% is landfilled, 5% goes to surface disposal, 0.6% is applied in forests and 21.9% goes to agriculture and grazing land. These figures might have changed over time; however, it is surprising that the speaker's estimates differ to that extent.

19. Transcript page 112, line 10:
Nobody is looking for these chemicals right now in food. Let's take a look what happens in food.
Slide 33: Biocides in food, drinking water, human milk, blood and urine

The speaker fails to inform us about any values or measurement for triclosan in food and fails to prove his speculation about a passage from soil to plants. Instead the speaker talks about child poisoning with very doubtful and old cases from hospitals. Food concentrations or other details about food supply are not given, although referenced.

Presented was **slide 38** as summary of reports and unpublished data, however, there is no food supply mentioned for triclosan. Triclosan in breast milk, human blood and urine has, as laid out before, nothing to do with food supplies. This is insinuated with this slide but certainly not substantiated with data.

20. Transcript page 115, line 3:
There is one study of triclosan in breast milk. Again, this is the bioaccumulation process of once it's in fat, it doesn't leave it and breast milk obviously has a high percentage of fat, about 4 percent, and we have made other detections of triclosan in breast milk.

In 2002 a small-scale Swedish study (Adolfsson-Erici et al. (2002) Triclosan, a commonly used bactericide found in human milk and in the aquatic environment in Sweden. Chemosphere 46, 1485-1489) was published claiming that traces of triclosan have been found in environmental and human breast-milk samples. Amongst others, five random specimens from a milk-bank were analyzed. Three had triclosan detected in trace amounts in the parts per billion (ppb) range. This concentration is more than 1000 times lower than proven safe levels for human intake. Therefore, the concentrations of triclosan reported in this study do not harm either mothers or breast-fed infants. Triclosan is not accumulated in the human body but readily metabolised and excreted via the urinary route.

An occurrence in breast milk samples may be due to the use of e.g. triclosan-containing toothpaste, resulting bloodstream levels and secretion from the lactiferous gland. An uptake from environmental sources can be safely excluded. The reported findings of triclosan in environmental samples* are without interrelation to the milk samples.

Studies to date have demonstrated that triclosan is safe and that it has multiple benefits in the prevention of harmful bacteria, e.g. against gingivitis. New research suggests a link between preterm, low birth weight babies and gingivitis during pregnancy against which the use of triclosan is recommended (Dörtbudak O, Eberhardt R, Ulm M, Persson GR (2005) Periodontitis, a marker of risk in pregnancy for preterm birth. J Clin Periodontol 32, 45-52)

21. Transcript page 115, line 12:
Finally, triclosan has been detected in human urine... There is so much going around that we actually excrete it again.

It is clear from the pharmacokinetics of triclosan that, once taken up by use of consumer products, it will be quickly eliminated from the human body in the urine. This detection is not any surprise. However, the reasoning that "there is so much going around" can be taken as alluding to a secondary intake resulting in urinary excretion. This can definitely be ruled out.

22. Presentation slide 39:

- Biocides persist in the environment: For triclosan, there are numerous studies and publications showing ready biodegradation.
- Biocides are produced faster than they degrade: For triclosan, this can certainly not be interpreted from any of the existing data, since removal levels are high in waste water treatment, outflow masses low, and degradation is going on in streams and soils.
- Biocides contaminate food supply: This has not been demonstrated by the speaker with any data.

Although the speaker very frequently mentions the mere detection of triclosan in different compartments and media, he fails to do a real mass balance or risk assessment. What is the risk biota encounter with the concentrations detected is a question which remains unanswered throughout the presentation, although relevant data and assessments exist (Reiss et al. 2002). Risk evaluations must be based on toxicological studies, proper NOAEL and margins of safety for humans and PNEC values for the environment, and a proper ecological systems approach which takes into account the real-world conditions in receiving rivers and soils.

23. Transcript page 159, line 1:
Dr. Taylor: Could you summarize the risk assessment studies on these compounds, have there been the risk assessment, for example, what is the NOEL?.

Dr. Halden clearly fails to name any of these details, neither the risk assessments being done in the US for the aquatic environment (Reiss et al. 2002) nor is able or willing to give NOEL-data represented in Orvos et al. (2002).

Other citations from the same speaker during the meeting were omitted because he reiterated the incorrect statements only in some variation. Most of them are covered by the above comment.