UNITED STATES DISTRICT COURT
DISTRICT OF UTAH, CENTRAL DIVISION

UNITED STATES OF AMERICA
V.
MAGNESIUM CORPORATION OF AMERICA, *et al.*

EXPERT REBUTTAL REPORT
OF
Dr. RICHARD L. DEGRANDCHAMP, Ph.D.

Regarding the Magnesium Corporation of America,
Rowley, Utah

Prepared for
U.S. Department of Justice
Environment and Natural Resources Division
Washington, D.C.

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1 INTRODUCTION

I previously conducted a toxicological evaluation and risk assessment for the manufacturing concern previously called the U.S. Magnesium LLC in Rowley, Utah, (the Facility). My results and conclusions were included in my expert report (dated 6 February 2007). This report presents my rebuttal responses to critiques of that report presented in the defense expert reports of Drs. Finley and Lyons. In addition to their critiques of my expert report, Drs. Finley and Lyons also present their independent analyses of health effects at the Facility. This rebuttal report presents a reevaluation of specific aspects of my earlier report, comments on their analyses, as well as rebuttals to their critiques.

2 SUMMARY OF REBUTTAL RESPONSES

2.1 Summary of Human Health Risks in the Remote Areas

I have carefully evaluated the analyses, supporting studies, and peer review publications submitted by Dr. Finley as part of his human health risk assessment (HHRA) for the Waste Management Units (WMUs) in the remote areas. Overall, I find his analyses supportive of his conclusions.

I, too, presented an HHRA as part of my expert report. However, my HHRA was prepared using standard default risk assessment assumptions based on readily available data and information. EPA specifically requested that I perform a default risk assessment and, therefore, I did not refine the risk estimates I presented in my expert report. In contrast, Dr. Finley was able to generate site-specific information by conducting Facility-funded studies. By incorporating the new information into his HHRA, he made reasonable and scientifically appropriate assumptions that ultimately lowered the risk estimates in many WMUs, but most importantly the waste ponds. Dr. Finley concluded the current and future health risks to workers in most WMUs in the remote regions of the Facility are at acceptable levels, and I agree with his conclusion. I also concur with Dr. Finley that unacceptable future risks may be associated with exposures in the central and main ditches, which are contaminated with high levels of dioxins and HCB. I have no additional comments on the human health risks in the remote areas.

2.2 Summary of Health Threats to Facility Workers

I have reviewed the defense expert reports critiquing my analysis and conclusions regarding exposures and health risks for Facility workers (or Facility cohort). After carefully considering their critiques and reevaluating my calculations and opinions in response to their critiques, I have concluded dioxin and HCB exposures and health risks are slightly *higher* than I previously reported. The following presents a summary of my rebuttal conclusions, many of which are based on background body burdens of dioxins and HCB presented in the NHANES database:

2.2.1 Dioxins

- The average body burden of dioxin TEQ (which represents the sum of dioxins and furans in this report) and HCB in the Facility cohort is more than 2 times background levels in the U.S. general population (41.5 ppt versus 19.0 ppt, respectively);

- The dioxin body burden of the maximum exposed worker is 175.9 ppt, which is more than 9 times the average background level (19.0 ppt) and greatly exceeds the maximum background level of 94.9 ppt;

- The *average* and *maximum* total dioxin TEQ body burdens [excluding dioxin-like PCBs (DL-PCBs)] in the Facility workers pose a total cancer risk of 8.2 per-one-thousand (8.2E-3) and 3.5 per-one-hundred (3.5E-2), respectively;

- The average and maximum *Facility-related* cancer risk (excluding background risks) is 1.1 per-one-thousand (1.1E-3) and 7.7 per-one-thousand (7.7E-3), respectively;

- Based on total dioxin TEQ exposure, the average and maximum Facility worker is exposed to 5 and 19 times, respectively, the maximum TDI safe exposure level (WHO-1998);

- The diabetes prevalence rate of 17% in the Facility workers is very high compared with the background rate of 6.7%, and it may be associated with Facility dioxin (and HCB) exposures.

2.2.2 HCB

- All 30 workers in the Facility cohort have high HCB body burdens compared with the U.S. general population, in which HCB is undetected;

- The *mean* HCB body burden levels measured in 2002and 2004 show an increased exposure for Facility workers;

- All 30 workers in the Facility cohort have HCB body burdens far in excess of the health-based body burden of 1.1 ppb, which is associated with immunotoxic effects; and

- HCB and dioxin body burdens are highly correlated in the Facility cohort, which proves Facility workers are exposed to both dioxin and HCB on a daily basis.

3 GENERAL REBUTTAL COMMENTS FOR FACILITY WORKERS

Drs. Finley and Lyons present separate and independent expert opinions regarding their interpretations of dioxin and furan body burdens and their associated health threats. It is noteworthy that their opinions are different on many key aspects of both the background analysis and toxicological assessment. Both Dr. Finley and Dr. Lyons are highly critical of the focus I placed on the "maximum" exposed individual in my earlier expert report. While I still firmly believe that all health professionals must ethically make an effort to protect *all* workers from toxic exposures in the workplace (and not just most of them), I now include both the average and maximum recalculated values in this report. These recalculations still show high exposure and health risks for Facility dioxin and furans.

Despite overwhelming evidence to the contrary, both defense experts conclude body burdens in Facility workers are within background levels for the U.S. general public *and consequently* there are no health threats to workers. Both these conclusions are unsupported by numerous facts and site-specific evidence that clearly show dioxins, furans, and HCB, which are the only Facility-specific chemicals of concern (COCs), are highly elevated in both the average and maximum exposed workers. Dr. Finley inappropriately includes dioxin-like PCBs (DL-PCBs) in the analysis even though there is no environmental or body burden evidence to show that workers are exposed to DL-PCBs in the Facility. In doing so, Dr. Finley 1) obscures the background analysis of facility exposures to dioxins and HCB, and 2) dilutes the true Facility-related health threats.

Neither expert has conducted any generally accepted statistical test in his evaluation of background conditions to determine if the Facility and background populations are different. Instead, they both simply make "rough," and inappropriate, non-statistically based comparisons of individual statistics. It is curious that they expend considerable time and effort to generate a sophisticated age-adjusted background dataset from the complex NHANES database, but stop well short of applying a rather simple and routine (parametric or nonparametric) statistical test requiring minimal time and effort. They also did not include in either report the limited information I would need to independently run the tests to verify their results. By not applying statistical tests to their datasets, relying instead on rough and inappropriate approximations, their opinions lack scientific merit. Furthermore, despite statements from both Drs. Finley and Lyons stating that they have conducted thorough and independent analyses using the *same* NHANES database, it is of great scientific importance that their results and statistics do not agree. That is, starting with the same NHANES database and with the same stated goals, they ultimately present

divergent and disparate statistics for the U.S. general population. Based on the very limited results they present, and lacking vital information about their respective approaches, it is impossible to confirm either expert is correct. I could not verify the extracted data from the NHANES database nor could I carry out the statistical analyses that need to be applied to determine if dioxin levels in the Facility cohort are statistically different from background.

The two defense experts use the same NHANES dataset but extract different data and generate different background statistics. Moreover, Dr. Lyons assumes the maximum exposed Facility worker is an artifact of sampling and labels him an "outlier." He makes this assumption but provides no evidence. He does not apply simple and routine statistical tests to confirm his assumption. The outlier test I applied not only clearly shows the individual with the highest body burden should not be considered an outlier, but clearly shows that he *cannot* be considered an outlier. That individual not only has the highest dioxin body burden, but has the highest HCB level as well. Moreover, dioxins and HCB are highly correlated in that individual, as well as in the entire Facility cohort. My analysis will show the body burden of dioxin and HBC in the maximum exposed individual are at precisely the levels they should be, based on exposure conditions at the Facility.

Both Dr. Finley and Dr. Lyons consider "background body burdens" to be synonymous with "safe body burdens." They assume that if they can simply state body burdens in Facility workers are not different from background levels, all other health-related problems vanish. To show this is a false assumption, I present strong and new evidence revealing subtle toxic effects occurring even in the general U.S. population at background levels of dioxins and HCB. Therefore, any additional exposures increase health risks to the workers and are unacceptable.

Many of Dr. Finley's critiques lack scientific merit or are focused on insignificant issues that were either irrelevant or had negligible impact on my results or conclusions. He critiques my use of an "inappropriate dataset," but he uses the same dataset to make similar comparisons. Some of his critiques led me to reanalyze a few of my calculations; these new results show even stronger scientific support for my conclusions. The dioxin body burdens I present in this report are slightly higher and the risk slightly elevated from my previous report.

Unlike the HHRA Dr. Finley conducted for the remote areas in which he used reasonable assumptions and followed a clear and appropriate scientific method, his background analysis for the Facility workers only obscures the true Facility-related exposures to dioxins and furans. Specifically, Dr. Finley includes

DL-PCBs in his analysis even though, as I will show, DL-PCBs have not been released by the Facility and are at background body burden levels in the Facility cohort.

For many of their critiques, both defense experts simply reiterate statements from the National Academy of Sciences (NAS 2006) review of EPA's 2003 Dioxin Reassessment. Dr. Finley relies so heavily on the NAS review that he excludes from consideration more applicable and relevant scientific reviews and analyses from *official* health agencies and organizations. This includes the National Toxicology Program (NTP; part of the Department of Health and Human Services) and the International Agency for the Research on Cancer (IARC; part of the World Health Organization). They also present misleading statements that do not capture the entire NAS conclusions and recommendations on many scientific issues.

Although the NAS (2006) review committee was made up of many highly regarded scientists, the NAS committee is an *ad hoc* committee that existed solely as a review committee to offer suggestions to EPA in order to improve EPA's dioxin reassessment report. In their report, the NAS scientists state many valid critiques of the EPA reassessment—most of which I agree with. However, unlike the defense experts' characterization that the report shows EPA was "wrong," NAS did not in fact condemn EPA's scientific approach but made many recommendations of ancillary studies that will ultimately strengthen EPA's conclusions. Many of the recommendations are not new and have been previously stated by many other scientists, including myself. In other words, NAS urges EPA to test other scientific approaches and consider alternate theories.

I did not follow, use, or state any of EPA's conclusions in either of my expert reports. Despite my conscious effort to avoid the controversial issues surrounding EPA's report, both Drs. Finley and Lyons attempt to color my health study as an EPA-based approach. For example, I did not use or even discuss the EPA-revised slope factor for dioxin (1E+6) in my toxicological evaluation, nor did I critique Dr. Finley's HHRA because he did not use it to calculate risks. Nevertheless, both experts mischaracterized my analyses and critiqued using slope factors based on a "low-dose extrapolation" model. Not only did I not use any such models for dioxin, but I also avoided relying on "animal data" (for which my analysis was also critiqued). In short, careful review of my analysis shows I used reasonable assumptions from diverse reports, studies, and reviews from many federal and international health agencies and organizations, while defense experts rely far too heavily on a single NAS review. It should be noted that the NAS review itself has not undergone scientific scrutiny or review by other scientists, and therefore should not automatically be considered the "gold standard."

In many instances, Dr. Finley correctly points out uncertainties in some of the studies upon which I relied. However, he does not acknowledge that—for better or worse—those studies represent the current state of the science, and there are no others available. One fact scientists can be certain of is that scientific uncertainty will always exist. In view of this fact, Dr. Finley does not propose using an alternate study with different results or even attempt to quantify the uncertainty in my analysis. In many instances, he just disregards the entire study.

Dr. Finley does not acknowledge some of the widespread uncertainty in the studies he cites that we now know to be highly pervasive in all past epidemiological studies. This uncertainty is much more global and is the likely reason dioxin studies and results have not been more consistent. Scientists now know that nearly all past studies suffered from misclassification of the non-dioxin exposed control, or reference, group. That is, there is no such thing as a "non-dioxin exposed population." Consequently, epidemiological studies have actually been measuring the difference between light dioxin exposures and heavy exposure where the actual dioxin-related difference in observed effects was artificially compressed. Several recent studies employing very clever scientific approaches to identify truly non-dioxin exposed populations show dioxin-related effects (such as diabetes) occurring at background levels in the general U.S. population. Despite this now obvious experimental flaw, I do not simply dismiss all past studies out of hand.

4 SPECIFIC REBUTTAL RESPONSES TO DR. FINLEY'S REPORT

Based on a thorough review of Dr. Finley's independent analysis and his critiques, I have reanalyzed the body burden data. I have concluded the following:

- The average and maximum total dioxin TEQ body burdens for Facility workers is now 41.5 ppt and 175.9 ppt (WHO 2005), respectively, which represents an increase from the 35.3 ppt and 142.5 ppt (WHO 1998) I presented previously;
- The revised dioxin TEQ body burdens strengthen the evidence that Facility workers are receiving significant dioxin exposure. The average worker body burden of 41.5 ppt is more than double the background concentration of 19.0 ppt. Moreover, the maximum of 175.9 ppt is much higher than the corresponding background level of 94.9 ppt;
- The only chemicals of concern for Facility worker exposures are dioxins, furans, and HCB;
- DL-PCBs are not COCs for evaluating worker exposures; and
- Including DL-PCBs in an analysis of Facility exposures only serves to obscure the true Facility-related exposures to dioxins, furans, and DL-PCBs, and their associated cancer risks and health threats.

4.1 Dioxin Body Burden

4.1.1 Revised Dioxin TEQ Body Burden for the Facility Cohort

Dr. Finley states that I compared the Facility cohort dioxin TEQ using WHO 1998 with the background data in Ferriby *et al.* that were based on WHO (2006). I did so because there were only minor changes in TEF values for dioxin and furans in the WHO 2005 update, as shown in Exhibit 1.

EXHIBIT 1: MINOR DIFFERENCES BETWEEN TEF VALUES: WHO 1998 AND WHO 2005

The International Programme on Chemical Safety (IPCS)

WHO UNEP

Compound	WHO 1998 TEF	WHO 2005 TEF*
chlorinated dibenzo-p-dioxins		
1,2,3,7,8-PeCDD	1	1
1,2,3,4,7,8-HxCDD	0.1	0.1
1,2,3,6,7,8-HxCDD	0.1	0.1
1,2,3,7,8,9-HxCDD	0.1	0.1
1,2,3,4,6,7,8-HpCDD	0.01	0.01
OCDD	0.0001	**0.0003**
chlorinated dibenzofurans		
2,3,7,8-TCDF	0.1	0.1
1,2,3,7,8-PeCDF	0.05	**0.03**
2,3,4,7,8-PeCDF	0.5	**0.3**
1,2,3,4,7,8-HxCDF	0.1	0.1
1,2,3,6,7,8-HxCDF	0.1	0.1
1,2,3,7,8,9-HxCDF	0.1	0.1
2,3,4,6,7,8-HxCDF	0.1	0.1
1,2,3,4,6,7,8-HpCDF	0.01	0.01
1,2,3,4,7,8,9-HpCDF	0.01	0.01
OCDF	0.0001	**0.0003**

* Numbers in bold indicate a change in TEF value

Reference - *Van den Berg et al*:
The 2005 World Health Organization Re-evaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-like Compounds

ToxSci Advance Access, 7 July 2006

Nevertheless, in response to Dr. Finley's critique, I recalculated the total Facility body burden TEQ-WHO 2005 (based on dioxins and furans) and present the revised TEQ body burdens in Exhibit 2. What is noteworthy about this table is that the TEQ level for each Facility worker was slightly increased, as was the average and maximum for the entire Facility cohort.

EXHIBIT 2: TOTAL DIOXIN TEQ IN FACILITY WORKERS: WHO 1998 AND WHO 2005

FACILITY WORKER	WHO 1998 FACILITY TOTAL DIOXIN-FURAN TEQ	WHO 2005 FACILITY TOTAL DIOXIN-FURAN TEQ
1	10.9	12.9
2	12.1	13.2
3	12.8	14.0
4	15.6	18.2
5	17.6	20.1
6	20.1	21.6
7	20.2	23.0
8	20.9	24.5
9	22.5	26.1
10	23.0	26.4
11	24.2	26.9
12	24.8	27.4
13	25.5	27.9
14	25.8	28.6
15	26.3	29.2
16	26.6	29.8
17	27.2	30.5
18	29.2	33.7
19	32.8	36.1
20	36.4	41.5
21	39.3	41.9
22	39.9	47.8
23	41.3	51.8
24	42.4	52.8
25	48.5	55.9
26	51.5	63.1
27	55.3	63.6
28	56.4	71.6
29	87.6	109.3
30	142.5	175.9
MEAN CONCENTRATION	**35.3**	**41.5**

All concentrations in ppt.

As shown, the average Facility cohort total dioxin TEQ was slightly increased from 35.3 to 41.5 ppt, and the maximum increased from 142.5 to 175.9 ppt. These new data do not significantly alter my expert opinion, but do strengthen the evidence that Facility workers are receiving significant dioxin exposures at the Facility. Evidence that clearly shows the Facility cohort dioxin body burden is significantly elevated over background is presented in Exhibit 3. More than 26 workers were higher than the average.

EXHIBIT 3: COMPARING FACILITY WORKERS WITH BACKGROUND BODY BURDEN USING WHO 2005

BODY BURDEN STATISTIC	FACILITY WORKER TEQ WHO 2005	BACKGROUND TEQ WHO 2005
Average	41.5	19.0
Maximum	175.9	94.9

All concentrations in ppt.

Background TEQ from Ferriby *et al.* 2006; Males 45-59 dioxin and furan TEQ.

The average Facility cohort body burden of 41.5 ppt is more than double the background concentration of 19.0 ppt (Ferriby *et al.* 2006). It also shows the maximum exposed worker with a dioxin level of 175.9 ppt is much higher than the corresponding maximum in the general U.S. background population, which is 94.9 ppt. The cancer risks and noncancer health hazards have increased concomitant with these increased body burden levels.

4.1.2 DL-PCBs Are Not COCs

Dr. Finley's analysis of dioxin body burdens is flawed and misleading because he includes dioxin-like PCBs in his analytical comparison with general U.S. background levels (in this report, DL-PCBs refer specifically to the 12 PBC congeners that have dioxin-like properties, it does not refer to PCBs in general) or non-dioxin like PCBs that I did not evaluate; note only 9 DL-PCBs were analyzed by NIOSH (2005).

Dr. Finley states that it is general practice to sum *all* dioxin like compounds when identifying Facility specific COCs and this is incorrect. Before they are summed into a total dioxin-like TEQ, a detailed analysis must first be conducted to determine which of the three dioxin-like groups, namely, dioxins, furans, and/or DL-PCBs are Facility-specific COCs. Facility-specific COCs are defined as contaminants that are produced and released during Facility manufacturing operations and have been detected in workers' bodies above background levels. DL-PCBs do not meet either of these 2 standards.

Simply put, DL-PCBs are not COCs and by, including them into his report, Dr. Finley obscures the analysis of the true Facility-specific COCs, which are dioxins, furans, and HCB. The following is a summary of the overwhelming evidence that DL-PCBs are not Facility-specific COCs and, therefore, should not be evaluated further:

- Production and release of DL-PCBs by the Facility is insignificant, and no soil, air, dust, or water sample collected in the Plant areas contains significant amounts of DL-PCBs;
- Body burdens in the Facility cohort are precisely at background levels, proving no exposures to DL-PCBs have occurred during their tenure of 25 years or so at the Facility;
- There is a strong correlation between body burden levels of dioxins and HCB, but no correlation between DL-PCBs and HCB in Facility workers' blood samples;
- DL-PCBs have not been detected in significant amounts anywhere in the remote areas of the Facility;
- Dr. Finley and MWH (defense contractors) expended considerable time and effort eliminating more than 50 chemicals from the HHRA as COCs that they concluded were not Facility-specific; Dr. Finley does not apply the same approach in his evaluation of Facility workers;
- Dr. Finley and MWH eliminated chemicals as COCs because they were at or below background levels and were clearly not Facility-related; Dr. Finley does not eliminate DL-PCBs based on this criterion for the Facility workers;
- Dr. Finley evaluated only a handful of COCs in his HHRA that he ultimately concluded were truly associated with Facility operations; and
- Dr. Finley did not evaluate any health risk for any chemical that was not a Facility-specific COC in his HHRA.

In stating it is "routine" to sum all dioxins, furans, and DL-PCBs in the total dioxin TEQ in identifying COCs, Dr. Finley has confused Step 1 with Step 2 of a typical toxicological assessment. These steps are as follows:

Step 1. Evaluate environmental data to identify individual Facility-specific dioxin like COCs that are produced and released by the Facility and are ultimately shown to be elevated in Facility workers' bodies.

Step 2. Conduct a toxicological assessment to quantify health threats posed by exposure (body burdens) to Facility-specific dioxin-like COCs (i.e., estimate cancer risk and noncancer health threats).

In Step 1, dioxins, furans, and PCBs are first evaluated to determine which group(s) are Facility-specific COCs. Chemicals not identified as Facility-specific are eliminated from further consideration. Only Facility-specific chemicals are investigated further to determine whether they are detected in Facility workers above background levels. In Step 2, cancer risk and health hazards are calculated based on total dioxin TEQ for Facility-related contaminants.

After careful evaluation of all Facility environmental and biological samples, I found no evidence of significantly elevated DL-PCBs anywhere in the facility. Furthermore, the DL-PCBs levels measured in workers' blood show they are precisely at background levels for the general U.S. general population.

Dr. Finley did not identify any significant levels of DL-PCBs in the remote areas, and he did not identify them as COCs. Despite the absence of DL-PCBs anywhere in the facility, he critiques my report stating:

> *The rationale that he provided for his decision to rely on the Ferriby et al. (2006) publication was that the total TEQ presented in the Patterson et al. (2004) was not based on the "conventional dioxin-like congeners" and the Ferriby et al. (2006) publication presents total dioxin TEQs for dioxins and furans separate from PCBs. The importance of this latter point is that Dr. DeGrandchamp has "concluded PCBs are not chemicals of concern for the Facility cohort (the levels measured in the Facility samples are not significant for exposure)." He provides absolutely no basis for this statement.*

This statement is incorrect on both points. DL-PCBs are *not* chemicals of concern at the Facility because even a cursory review of environmental data (i.e., soil, dust, water, air, etc.) shows DL-PCBs have not been produced by the facility.

DL-PCBs are not significantly elevated anywhere within the Facility. Simply put, DL-PCBs have not been detected at significant levels in the melt reactor or electrolytic buildings, nor have they been detected in the remote areas away from the plant, which is a reflection of what is being produced inside the plant.

They have not been appreciably detected in any air, dust, soil, or water sample. As for providing *"absolutely no basis for this statement,"* I have been clearer in my expert report stating:

> *Lastly, I have disregarded the toxic effects of PCBs, which are also produced as byproducts and released during production. Based on the relative concentrations that have been measured at the Facility, I have concluded that PCB exposures do not merit the same attention that is necessary for dioxin and HCB exposure.*
>
> *Secondly, I have concluded PCBs are not chemicals of concern for the Facility cohort (the levels measured in the Facility samples are not significant for exposures); they should not be included in the total dioxin TEQ calculations. The Ferriby study provides this specific information.*

Dr. Finley states:

> *However, NIOSH clearly evaluated PCBs in their HHE and included them in their TEQ calculations because they believed them to be important (NIOSH HHE, Tables 5-9).*

Even if this statement *were* true, it is not a scientific explanation for including DL-PCBs in the total TEQ. NIOSH analyzed for DL-PCBs to determine *if* exposures to DL-PCBs *are* occurring. The results prove exposure to DL-PCBs is *not* occurring. Thus, in addition to the fact that Dr. Finley's statement lacks scientific rigor, it is an incorrect statement: In fact, NIOSH intentionally excluded DL-PCBs from the TEQ calculations. There are 3 tables in which NIOSH (2005) presents the total TEQ, and none of them contain PCBs. Exhibit 4(which is NIOSH Table 7) shows the results for dioxin, furan, and PCB groups are presented individually. As shown, the mean dioxin (PCDD) and furan (PCDF) levels are 11.6 and 23.7 ppt respectively. Consequently, the total TEQ of 35.3 ppt only represents dioxins and furans and *not* DL-PCBs. If it did include PCBs, the total would be 40.8 ppt (based on Exhibit 10).

EXHIBIT 4: NIOSH TABLE 7 SHOWING DL-PCBS ARE EXCLUDED FROM TOTAL TEQ

Table 7
HETA 2004-0169-2982
U.S. Magnesium Corporation Rowley, Utah
August 2004
Means of PCDDs, PCDFs and PCBs by Department

	PCDDs		PCDFs		PCBs*	
	pg/g lipid*	TEQ†	pg/g lipid	TEQ	ng/g lipid‡	TEQ
Cell Brick	287.1 ± 109.7	8.7 ± 3.2	217.8 ± 205.9	12.7 ± 6.6	13.4 ± 1.3	4.8 ± 1.3
Electrolytic	536.3 ± 312.5	13.1 ± 6.2	614.2 ± 270.9	20.3 ± 8.8	17.2 ± 1.3	6.1 ± 1.4
Maintenance	348.7 ± 68.4	12.7 ± 6.6	707.7 ± 679.3	47.6 ± 42.2	15.0 ± 1.4	5.5 ± 1.4
Reactor	320.2 ± 183.7	13.1 ± 3.9	340.9 ± 153.6	24.6 ± 8.3	15.2 ± 1.4	6.1 ± 1.5
Total	371.4 ± 209.6	11.6 ± 5	442 ± 398.5	23.7 ± 22.7	15.0 ± 13.1	5.5 ± 1.4

Dr. Finley states:

> *Because the numbers of congeners reported in each of the three studies are different, Dr. DeGrandchamp makes an inappropriate comparison of dioxin TEQ values between the three studies in Exhibit 3. Specifically, he compares TEQ values reported in the NIOSH HHE for Facility workers (**which I believe includes PCDDs + PCDFs + 3 of the 4 coplanar PCBs*** **[emphasis added]** *to the reference values provided by Patterson et al (2004) – which include some PCBs, to the reference values provided by Ferriby et al (2006) – which do not include PCBs.*

Dr. Finley's statement, "I believe the PCDDs + PCDFs + 3 of the 4 coplanar PCBs" are included in the total TEQ from the NIOSH report must be a misstatement because dioxins, furans, and PCBs were presented separately in the NIOSH report. Furthermore, the total TEQ in other NIOSH tables do not contain DL-PCBs. However, even if Dr. Finley had questions about Tables 5 and 6, Table 7 presented separate concentrations of dioxins (PCDD), furans (PCDFs), and PCBs. Additionally, Dr. Finley states

he conducted a thorough and independent statistical analysis, so he must know what dioxin congeners he included in his own analysis.

The following sections provide unequivocal evidence that DL-PCBs are not COCs and should not be forced into the analysis.

4.1.3 DL-PCBs Are at Background Levels

An analysis of the body burden levels of DL-PCBs in Facility workers shows they have the same background level of DL-PCBs as the U.S. general population. The average DL-PCBs body burden concentration in Facility workers is 11.4 ppt (based on WHO 2005). The corresponding background body burden for males aged 45-59 in the U.S. general population is 11.2 ppt (Ferriby *et al.* 2006). Since the Facility worker's body burdens are the same as background levels, workers have not been exposed to DL-PCBs at the facility.

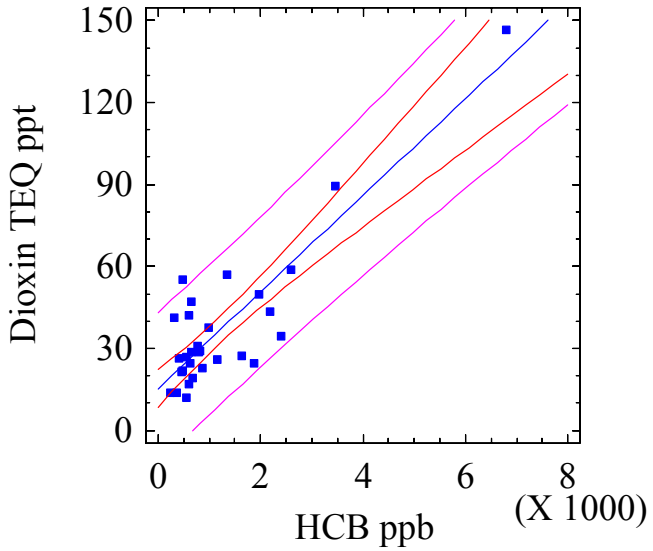
4.1.4 There is No Correlation Between DL-PCBs and HCB

Analysis of the association between dioxins and HCB body burden levels reveals a very strong correlation between dioxins and HCB in Facility workers' blood samples. In contrast, no correlation between DL-PCB and HCB exists. As discussed in greater detail in Section 4.6, the Third NHANES report clearly shows HCB is not detected in the U.S. general population. Therefore, any HCB detected in Facility workers must be from exposures at the Facility.

Environmental samples show that dioxins and HCB are not only detected in high concentrations, but are always detected together in the same sample. This means that dioxins and HCB are co-localized, and Facility workers experience simultaneous dioxin and HCB exposures throughout the day. That is, workers are exposed to both contaminants through inhalation, absorption through the skin, and via inadvertent ingestion. Since HCB body burden is a clear measure of exposure to Facility-related contaminants (there is no background body burden), there should be a correlation between HCB and other COCs that are being produced by the Facility. I conducted a linear regression analysis to determine how strongly HCB and dioxin are correlated in each individual. That is, since they are produced together and are co-localized, they should be strongly associated in workers bodies. I tested this assumption by plotting the concentration of each worker's HCB and dioxin body burden levels to determine if the ratios between the 2 contaminants are constant throughout the cohort. Clearly, they are. In Exhibit 5, each point represents a worker and the blue line represents a constant ratio between dioxin and HCB body

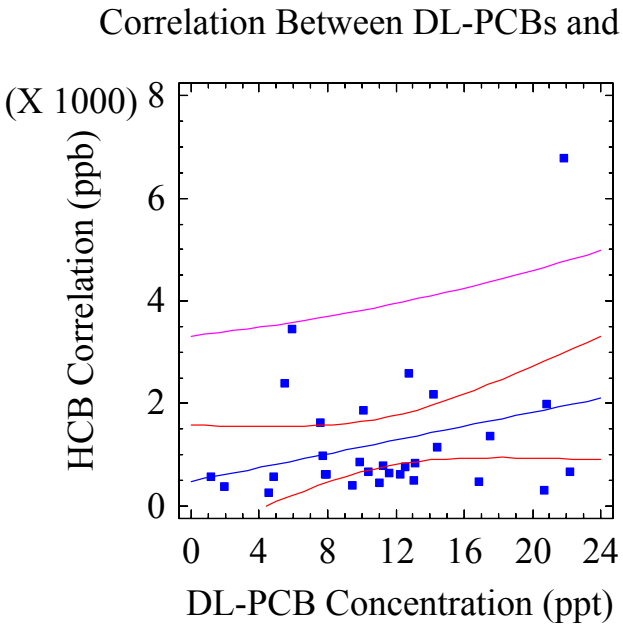
burdens. The correlation coefficient for dioxin and HCB in Facility workers is 0.87 (r-squared 77.3), which is very high. The interpretation of this analysis is that although the absolute body burdens of HCB and dioxins in each worker are different, the *ratio* between dioxins and HCB is the same for all workers.

EXHIBIT 5: FACILITY WORKER BODY BURDEN— HIGH CORRELATION BETWEEN DIOXIN AND HCB



In stark contrast to the strong correlation between HCB and dioxin, the linear regression presented in Exhibit 6 shows no correlation between DL-PCB and HCB. The correlation coefficient between DL-PCB and HCB is only 0.29, which indicates no correlation between the 2 compounds. The interpretation of this statistic is that Facility workers are being exposed to dioxins and HCB released by the Facility, but are not being exposed to DL-PCBs. For each incremental increase in HCB body burden, the PCB levels remain the same. The reason is simple; workers are not being exposed to DL-PCBs at the Facility.

EXHIBIT 6: FACILITY WORKER BODY BURDEN— NO CORRELATION BETWEEN DL-PCB AND HCB



4.1.5 Reduced DL-PCBs Contribution in Facility Workers

DL-PCBs contribute approximately 37% to the total dioxin TEQ in the U.S. background population. Therefore we would expect that DL-PCBs contribute to the dioxin TEQ in the Facility cohort. However, Dr. Finley reasons that simply because DL-PCBs contribute to the total TEQ, DL-PCBs should be considered COCs and be added to the TEQ, as though this is a unique finding.

In fact the opposite is true. The contribution of DL-PCBs in the Facility cohort is significantly *less* than we would expect based on the contribution of DL-PCBs in the background population, which indicates DL-PCBs are not COCs.

Dr. Finley states:

> *According to Table 9 in the NIOSH HHE Report, PCBs account for an average of 17.7 % of the total TEQ (based on the sum of mean values reported in Table 9) and may account for up to*

41.5% of the total TEQ (based on the sum of maximum values reported in Table 9). Clearly, the contribution of PCBs to the total TEQ is not only variable between individuals, but may also contribute significantly to the total TEQ and therefore should be included in the estimation of the TEQs for the US Magnesium workers. This conclusion is further supported by my review of the percent contribution of PCBs to the total TEQ based upon review of the individual NIOSH HHE data (see Section 4.3).

Dr. Finley neglects to mention that the contribution of DL-PCBs in the U.S. background population is 37% (Ferriby et al 2006). Thus, the contribution of 17.7% that Dr. Finley calculates is less than half the contribution in background. That is, there is a precipitous drop in the DL-PCB contribution because only dioxins and furans are increased. DL-PCB levels remain at background levels. This finding is shown in Exhibit 7.

EXHIBIT 7: PERCENT CONTRIBUTION OF DL-PCBS IS DECREASED IN FACILITY WORKERS

GROUP	TEQ DIOXINS AND FURANS	TEQ DL-PCBs	TOTAL DIOXIN, FURAN, AND DL-PCB TEQ	PERCENT DL-PCBs IN TOTAL DIOXIN TEQ
U.S. Background	19.0	**11.2**	30.2	37% (11/30*100)
Facility Workers	41.5	**11.4**	52.0	22% (11/30*100)

All concentrations in ppt.

Background TEQ From Ferriby *et al.* 2006; Males 45-59 dioxin and furan TEQ.

In Facility workers, the dioxin and furan TEQ body burden increases from 19.0 to 41.5 ppt (first column) while the DL-PCB levels remain essentially unchanged from a background level of 11.2 ppt (second column). When the TEQ is calculated based on dioxins, furans, and DL-PCBs (as shown in the third column), the contribution of DL-PCBs to the total TEQ is decreased from 37% in the background to 22% in the Facility workers (fourth column).

4.1.6 Diluting Worker Exposures with DL-PCBs

The above sections provide evidence to show DL-PCBs are not COCs. When they are included, they serve only to obscure Facility-related exposures to dioxins. Exhibit 8 shows the dilution effect when DL-PCBs are included.

EXHIBIT 8: COMPARING FACILITY WORKERS WITH BACKGROUND BODY BURDEN USING WHO 2005

	FACILITY-SPECIFIC RELEASES NO DL-PCB		DILUTING FACILITY RELEASES WITH DL-PCBS	
GROUP	**TEQ DIOXINS-FURANS**	**PERCENT INCREASE**	**TEQ DIOXINS-FURANS AND DL-PCBS**	**PERCENT INCREASE**
U.S. Background	19.0		30	
Facility Workers	41.5	**120%**	53	**77%**

All concentrations in ppt.

Background TEQ From Ferriby *et al.* 2006; Males 45-59 dioxin and furan TEQ.

As shown, the *average* dioxin and furans TEQ body burden in Facility workers is 120% higher than background levels. However, when DL-PCBs (which are at background levels) are added to the TEQ, the increase in body burden artificially drops to 77%.

4.1.7 I Relied on the Appropriate Background Levels

It is well known that dioxin body burden increases with age. Dr. Finley correctly states background dioxin TEQ levels should solely be based on males aged 40-49 years for comparison to the Facility cohort. I agree with him, but the Ferriby et al. (2006) study which we both relied on only presented information for males aged 40-49.

He goes on to say my analysis is now flawed because I used the Ferriby et al. study and not the "raw" NHANES database. His opinion has apparently changed from the first analysis in which he stated:

> *Approximately one year after the NIOSH HHE was completed, Ferriby et al (2006) published a rigorous evaluation of the PCDDIF and dioxin-like PCB data reported in the Third National Report on Human Exposure to Environmental Chemicals which was part of the 2001-2002 National Health and Nutrition Examination Survey (NHANES) of the United States population. There are several advantages of using the summary statistics from the 2001-2002 NHANES study presented in Ferriby et al (2006).*

He further alleges that that there is a significant difference between the statistics he generated from the NHANES data for males aged 40-45 and those presented in the Ferriby et al study. However, since he does not provide the NHANES data or any basic statistical descriptors such as the mean and standard deviation I cannot verify his findings. It would be surprising to find any significant difference between the 19 ppt reported in Ferriby et al. from those calculated by Dr. Finley from the NHANES dataset since only 3 men in the Facility cohort were slightly younger than 45 years of age (40-59 years of age). It also should be noted that after critiquing my use of the Ferriby et al. study, Dr. Finley relies on it for other parts of his analysis. Additionally, Dr. Finley has used age groupings that are clearly inappropriate for the Facility cohort because he used background data for men aged 30-44 and there are no Facility workers who were aged 30-40. The only difference between what Dr. Finley used in his first analysis and my previous analysis is that he used the wrong table from the Ferriby et al. study. That is, he used the table that included DL-PCBs.

Dr. Finley states that I have not included males aged 40-59, which shows I may have slightly *underestimated* exposures and cancer risk for the Facility workers. As I stated previously, I thought Dr. Finley had concluded the Ferriby et al. (2006) study presents the best peer-reviewed representative background data for the general U.S. population. He now states I should have used the NHANES dataset (which is what Ferriby et al. used) to extract more precise background body burdens.

I carefully evaluated the Ferriby *et al.* (2006) datasets before using the numbers in my expert report. I concluded that I would be slightly *underestimating* exposures and cancer risks because there were only 3 workers who were slightly younger than 45, but the difference would be insignificant. Moreover, including the 3 younger workers would increase the difference between the background and Facility body burdens. I decided to base my opinion on the Ferriby *et al*. (2006) study because it was important that Dr.

Finley and I use the same reference source, and it is the best available peer-review study available. It is unclear why Dr. Finley would critique such an insignificant part of my analysis. I note that although he critiques my analysis, he does not quantify the difference. I have concluded that there is no appreciable difference.

Instead of conducting routine and simple statistical analyses, Dr. Finley makes what he calls rough comparisons of "upper-bound" levels. Generally accepted statistical comparisons are based on the mean concentrations. By any comparison, however, the average Facility cohort body burden is double background levels which shows significant exposure to dioxins and furans.

Dr. Finley states:

> *Dr. DeGrandchamp relied upon inappropriate comparisons. Specifically, he compared the maximum TEQ from the Facility cohort to the mean TEQ for NHANES to determine if Facility workers as a whole had blood levels that were above levels observed in the general U.S. population. Dr. DeGrandchamp suggests that because risk assessment/management policy is based on the reasonable maximum exposed individual, that the health assessment should therefore be based on the highest level reported in the HHE. This is his justification for comparing the maximum value observed in the Facility cohort to the mean value in NHANES. This is clearly inappropriate as levels observed in the general U.S. population are characterized by a range of values just as is the Facility cohort.*

This is a mischaracterization of my analysis. I succinctly stated the 2 objectives of my analysis of dioxin exposures in Facility workers. The first was to determine if exposures to dioxins and HCB had occurred in the Facility worker cohort. The second objective was to determine if those exposures are associated with increased toxic health effects. Dr. Finley states that I compared:

> *..the maximum TEQ to the mean of the N maximum TEQ from the Facility cohort to the mean TEQ for NHANES to determine if Facility workers as a whole had blood levels that were above levels observed in the general U.S. population…This is his justification for comparing the maximum value observed in the Facility cohort to the mean value in NHANES.*

What I actually stated in my expert report was:

> *I reached two conclusions based on Exhibit 3. The first is that the entire Facility cohort has dioxin and furan body burdens well above background levels. For example, the average for the Facility cohort is about two times background body burdens.*

Furthermore, I am unclear where Dr. Finley sees the statement where I "justified" comparing the "maximum" Facility blood level to the mean value of background. What I stated with regard to the maximum blood level in the cohort was:

> *The second is that the individual with the highest body burden has a level that is about 7.5 times the average background body burden. Moreover, the body burden for this individual is significantly higher than the maximum in either the Patterson et al. or Ferriby et al. background population.*

This statement simply provides perspective on the highest body burden in a *single* individual. I made no inferences or extended *his* blood level of 147 ppt to represent the entire population. As I indicated, the sentences above refer only to an individual and not the entire population.

Dr. Finley states:

> *When determining if individuals are potentially different from the general U.S. population, standard practice is first to compare to the 95th percentile of NHANES.*

It is standard practice for comparing individuals; it is not standard practice for comparing a group of people such as the Facility cohort. It is not clear why Dr. Finley is focusing on determining whether *individuals* are potentially different from the general U.S population. First it is clear, even without applying statistics that the maximum exposed individual has a body burden that is far in excess of background. As I stated earlier, and as shown in Exhibit 3, the maximum body burden of a Facility worker was 174.9 ppt compared with a maximum of 94.9 ppt in the background population (Ferriby *et al.* 2006). Secondly, the central issue is whether, as a *group* of 30 individuals, the mean body burden in the Facility-cohort is elevated compared to the background group.

To determine if the Facility cohort as a whole is being exposed to dioxins and HCB, I evaluated the *entire* Facility cohort. This population was then compared with background reference levels for which I used the Ferriby *et al.* (2006) results, as Dr. Finley and I both agreed was representative and robust. I should

first state that I thought it would be obvious by a simple side-by-side comparison that the difference between the mean Facility cohort concentration and the mean in Ferriby *et al.* was so large that it was simply not an issue. That is, the *mean* dioxin level in the Facility cohort is more than *twice* the background body burden. With such a large difference, there is no need for statistics since they are only needed to detect small differences between populations, and then scientists generally refer to them as "statistical" differences. When a difference between the mean or average concentration is so large, as it is in this case, statistics are unnecessary. However, from Dr. Finley's statement, he believes that there is no difference between the Facility workers and background levels, so I will explain.

To determine whether there are differences in 2 populations, it is *always* standard statistical practice to determine whether the population means (or another central statistic similar to the mean) are statistically different. The mean is always used to conduct statistical tests in comparing populations because it is the least biased statistic with the most confidence that best represents the entire population. The tails of the population distribution at the high and low ends (i.e., the 95^{th} percentile or the 5^{th} percentile) are never used to determine if population means are different. This is because they only represent a small fraction of the population. The mean is the best descriptor of the entire population and is the least influenced statistic. For example, adding another datum to a group of 30 data will not greatly change the mean. Any comparison of values to the 95^{th} percentile is just that—a simple comparison of a single value. However, inferences and conclusions as to whether there are differences between populations cannot be made based on such a simple comparison.

Although there are dozens of statistical tests, the two most commonly applied statistical tests for population differences are the Student's t-Test and Wilcox Rank sum test. In using statistical tests, scientist state a "null hypothesis," which is simply that the difference between 2 population means is zero, meaning that they are statistically the same. In this case, the null hypothesis is that there are no differences in the means of the Facility cohort and background (Ferriby *et al.* 2006) as Dr. Finley contends. The Ferriby *et al.* study provides the necessary statistical information to determine whether the mean of the Facility cohort is statistically the same or different from the mean representing background they report. Neither the NIOSH nor the Ferriby *et al.* study presents the variance for the group to perform a statistical test, but a determination of whether the mean for the Facility cohort is different from the mean from the Ferriby *et al.* study is possible. In Ferriby *et al.* (2006; Table 1), the mean concentration of dioxins-furans for the age-adjusted background group is 19.0 ppt with a 95% confidence limit of 15.5 to 22.6 ppt. The interpretation of the 95% confidence limit is that they bracket the upper and lower concentrations of what the mean concentration could be for a background dataset. For example, if we had

100 different small groups of cohort groups from the general population and we compared the mean concentration to the 95% confidence limit, 95 times out of 100, the calculated mean for those groups would fall into the range of 15.5 to 22.6 ppt. Applying this statistical approach to the Facility cohort clearly shows the mean body burden of 41.5 ppt is far outside the background range of 15.7 to 22.8 ppt, and the *only* conclusion is that the Facility cohort is statistically different from background levels.

Dr. Finley presents an analysis of total dioxin TEQ based on dioxins, furans, and DL-PCBs. As I have previously stated, including DL-PCBs when they are irrelevant to the question of whether Facility workers have been exposed to uncontrolled releases of dioxins and furans obscures the analysis.

4.2 Dioxin-Related Cancer Risk

I have recalculated the dioxin-related cancer risks for the Facility workers based on the slightly revised Facility TEQ body burdens using WHO 2005 TEFs in response to Dr. Finley's critique. In addition, I have compared the revised Facility body burden TEQs to the body burdens that have been shown to produce a 1% increase (over background levels) in cancer. This body burden is referred to as an ED_{01} body burden and has been reported in several peer-reviewed published studies. The following summarizes the recalculated cancer risks:

- The *average* and *maximum* exposed Facility workers have total cancer risks of 8.2 per-one-thousand (8.2E-3) and 3.5 per-one-hundred (3.5E-2), respectively, based on total body burden;
- The average and maximum *Facility-related* (subtracting background) risk for the average and maximum exposed workers is 1.1 per-one-thousand (1.1E-3) and 7.7 per-one-thousand (7.7E-3), respectively; and
- In addition to the calculated cancer risks, twenty-six of the 30 Facility workers have body burdens in the range of published ED_{01} body burden levels and 8 workers have body burdens that *exceed* the maximum $ED_{01.}$

4.2.1 Updated Facility Worker Cancer Risks Are Higher

In response to Dr. Finley's critique that I used WHO1998 TEF values to calculate the dioxin TEQ to derive cancer risks, I have recalculated risks for the Facility cohort. The results are presented in Exhibit 9 and show that the average and maximum *Facility-related* (subtracting background) risk for the average and maximum exposed workers is 1.1 per-one-thousand (1.1E-3) and 7.7 per-one-thousand (7.7E-3), respectively. These risks are far above acceptable levels as described by EPA (1994) and discussed by Dr. Finley in his human health risk assessment for the remote areas.

EXHIBIT 9: DIOXIN-RELATED CANCER RISK FOR USM WORKERS BASED ON WHO 2005

FACILITY WORKER	DIOXIN-FURAN BODY BURDEN	TOTAL CANCER RISK (INCLUDING BACKGROUND)	TOTAL SITE-RELATED CANCER RISK (EXCLUDING BACKGROUND)
1	12.9	2.5E-03	-
2	13.2	2.6E-03	-
3	14.0	2.7E-03	-
4	18.2	3.6E-03	-
5	20.1	4.0E-03	4.6E-05
6	21.6	4.2E-03	1.2E-04
7	23.0	4.5E-03	1.9E-04
8	24.5	4.8E-03	2.6E-04
9	26.1	5.1E-03	3.4E-04
10	26.4	5.2E-03	3.5E-04
11	26.9	5.3E-03	3.8E-04
12	27.4	5.4E-03	4.0E-04
13	27.9	5.5E-03	4.3E-04
14	28.6	5.6E-03	4.6E-04
15	29.2	5.7E-03	4.9E-04
16	29.8	5.8E-03	5.2E-04
17	30.5	6.0E-03	5.6E-04
18	33.7	6.6E-03	7.1E-04
19	36.1	7.1E-03	8.3E-04
20	41.5	8.2E-03	1.1E-03
21	41.9	8.2E-03	1.1E-03
22	47.8	9.4E-03	1.4E-03
23	51.8	1.0E-02	1.6E-03
24	52.8	1.0E-02	1.7E-03
25	55.9	1.1E-02	1.8E-03
26	63.1	1.2E-02	2.2E-03
27	63.6	1.2E-02	2.2E-03
28	71.6	1.4E-02	2.6E-03
29	109.3	2.1E-02	4.4E-03
30	175.9	3.5E-02	7.7E-03
AVERAGE CANCER RISK		**8.2E-03**	**1.1E-03**

All concentrations in ppt.

I summarize the rationale and supporting evidence for my scientific approach in this section and explain why the cancer risk estimates in Exhibit 9 are correct and reasonable based on the existing state-of-the-science. As background, Drs. Finley and Lyons have both made the following critiques:

1. I have incorrectly relied on data from animal studies.
2. The human studies I cite are somehow unreliable and involve few numbers of people.
3. The results and conclusions from different dioxin studies are inconsistent.

These broad critiques do not apply to my analyses because:

1. The three cohort studies I rely on are human studies.
2. They involve more than 6,000 people.
4. All 3 studies had very similar and consistent results and findings.

4.2.2 There is Strong Supporting Evidence for Cancer Risks

Despite the differences in research groups, country of exposure, diverse workers exposed, and scientific methods employed, the 3 cohort studies yield very consistent results considering the size and complexity of the studies.

- All three studies have undergone substantial national and international peer review;
- A meta-analysis, in which the results from all three studies were combined (Crump *et al.* 2003), supports the overall conclusions of the three studies;
- There are no other comparable and competing studies that have ever been conducted, and Dr. Finley does not propose relying on other group of epidemiological studies that are more robust and would provide a better estimate of cancer risk.
- Dr. Finley is correct that the NAS (2006) dioxin review was critical of EPA's model used for low-dose extrapolation to derive the revised (and controversial) new cancer slope factor for dioxin. However, that critique does not apply to my analysis. I did not use a low-dose extrapolation model, as was suggested by Drs. Finley and Lyons. It was not necessary because the Facility blood concentrations were higher than levels reported in the three cohort studies.
- The NAS (2006) review is a compendium of good suggestions to improve the science. It is not a condemnation of EPA results and conclusions because they are "wrong." I concur with many of the recommendations of the report. If EPA follows the recommendations, it will strengthen the scientific support and justification for EPA actions. Ultimately, however, there is no current

evidence to indicate that if EPA adheres to the NAS recommendations, the EPA conclusions will significantly change.

Dr. Finley states:

> *The theory that cancer risk should be based on excess exposure or body burden (i.e., that which is above background) is appropriate; however, such an adjustment is not necessary in the case of the Facility cohort because all workers are within range observed for the general U.S. population. Specifically, Dr. DeGrandchamp chose to base his risk calculations on the highest observed body burden in the NIOSH HHE cohort (147 ppt), but because this body burden was within the range of concentrations observed in 40-59 year males in the general U.S. population, it is not appropriate to adjust this body burden.*

This is an incorrect statement. As I have shown in the recalculated results, the average body burden of the Facility worker is far above background levels for dioxins and furans as is the maximally exposed Facility worker. These higher body burdens translate into a slightly higher cancer risk. When the total dioxin body burden is considered by adding background exposures to Facility work-related exposures, the cancer risk is very high.

Dr. Finley states:

> *It was also inappropriate for Dr. DeGrandchamp to assume a default value of 25% body fat.*

It is standard toxicological practice to assume approximately 20% to 25% of body weight is fat. Obviously, there is a range in the U.S. population; however, minor changes in fat percentage would have little effect on my analysis or my opinion. EPA (2003) concluded in its report that a value of 25% represents the average:

> *Use of steady-state body burdens also has some limitations. In order to estimate steady-state body burdens from lipid-adjusted tissue concentrations, an assumption of the percent body fat must be used. In the reassessment, a value of 25% has been used for humans. It should be noted that there are human populations with body fat compositions as low as 10% and greater than 35%.*

Dr. Finley states:

> *The results in Table 5-6 of the Dioxin Reassessment (USEPA 2003) indicate that the set of plausible ED01 values spans at least one or two orders of magnitude for the Becher et al. (1998) study and the Ott and Zober (1996) study. Additionally, examination of Exhibit 4 indicates that the choice of model also has a substantial impact on the point of departure.*

It is not clear what Dr. Finley is referring to—the values in the Table 5-6 or the values that I used in my analysis. The ED_{01} values that I used in my calculations from Exhibit 4 in my report were 18.6, 32.2, and 50.9 ppt. As I mentioned earlier, these values are exceptionally close considering the complexity and number of variables in the study. There is only about a 2.5 fold difference between the ED_{01} values I used in my assessment. What I did not stress in my expert report, but now seems necessary to add, is that I could have used 1.38 and 5.97 from Exhibit 10 to *increase* cancer risks, but I thought a more measured approach was warranted.

EXHIBIT 10: EXHIBIT 4 OF MY EXPERT REPORT

Study	Model and Sex	ED_{10}	ED_{05}	ED_{01}	Unit excess risk for 1 ppt body burden above background
Steenland et. al, (2001)	power male	500 (46.4, 2.91 x 10^7)	33.9 (8.23, 1.59 x 10^4)	1.38 (0.71, 8.95)	0.0079 (0.0027, 0.0132)
	power female[1]	1315 (84.4, 4.5 x 10^8)	64.5 (12.6, 2.50 x 10^4)	1.84 (0.92, 14.9)	0.0064 (0.0022, 0.0107)
	piecewise linear male	• (92.9, •[3])	83.6 (51.8, •[3])	18.6 (11.5, 48.3)	0.00052 (0.00020, 0.00084)
	piecewise linear female[2]	•[8] (108.9, •[3])	100.7 (62.39, •[3])	23.1 (14.3, 59.8)	0.00042 (0.00016, 0.00067)
Becher et al., (1998)	power-male	120.3	41.17	5.971	0.0018
	power-female[4]	170.9	55.44	7.580	0.0014
	additive-male	192.8	93.35	18.22	0.00055
	additive-female[5]	239.1	116.2	22.75	0.00044
	multiplicative-male	258.9	144.4	32.16	0.00030
	multiplicative-female[6]	304.4	173.8	39.82	0.00024
Ott and Zober (1996)	multiplicative-male	411.7 (201.9, □)	229.0 (112.3, □)	50.9 (25.0, □)	0.00019 (0, 0.00039)
	multiplicative-female[7]	478.0 (234.4, □)	272.1 (133.4, □)	62.1 (30.5, □)	0.00015 (0, 0.00032)

Dr. Finley states:

> *The National Academy of Science (NAS) had a number of criticisms related to use of an ED01 in their review of the USEPA Dioxin Reassessment (NAS 2006):*

Following this statement, Dr. Finley goes on to repeat a list of critiques in the NAS review. I agree with most of the critiques, however most do not apply to my analysis. For those that do apply, I have responded accordingly. For example, knowing that there is some variability in reported ED_{01} body burdens, I analyzed the *range* of possible values and did not simply default to the "worst-case scenario." I stated as much in my expert report:

> *As discussed, there are three different studies that present a range of central tendency values for ED_{01} which are presented in Exhibit 4. These values are 18.6 ppt (Steenland et al. 2001), 32.2 ppt (Becher et al. 1998), and 50.9 ppt (Ott and Zober, 1996). After reviewing each study, I concluded that, instead of calculating an average ED_{01} values from these three studies, it would be better to calculate a range of cancer risks by using the highest and lowest ED_{01}. I adopted this approach to avoid introducing unnecessary uncertainty into my analysis. In fact, this source of uncertainty was the basis of another NAS critique directed at the EPA reassessment report.*

I should further respond to Dr. Finley's critiques to show my approach and results are reasonable. First, I did not use the lowest ED_{01} in Exhibit 10, which was 1.38 ppt. If I had, I would have concluded *all* 30 workers have blood levels *far* above the ED_{01}. In fact, the maximum exposed worker would have a level more than 150 times the lowest ED_{01}. Instead I not only used *maximum* ED_{01}s from each of the 3 studies, but I used the entire range of maximum ED_{01}s. It is important to stress that there aren't just a few Facility workers whose blood levels fall within the range of maximum ED_{01}s of 18.6-50.9 ppt. Rather, 26 of the 30 fall within that range and 8 *exceeded* the maximum ED_{01}. Exhibit 11 shows these findings. Workers numbered 5-22 are within in the ED_{01} range while workers numbered 23-30 exceeded that range.

EXHIBIT 11: FACILITY WORKERS WITH BLOOD LEVELS FALLING WITHIN OR ABOVE THE RANGE OF ED01 LEVELS

FACILITY WORKER	FACILITY BLOOD LEVELS (WHO 2005) THAT FALL WITHIN OR EXCEED THE RANGE OF 18.2-50.9 ED_{01}
1	12.9
2	13.2
3	14.0
4	18.2
BODY BURDENS IN THE RANGE OF 18.2-50.9 ED_{01}	
5	20.1
6	21.6
7	23.0
8	24.5
9	26.1
10	26.4
11	26.9
12	27.4
13	27.9
14	28.6
15	29.2
16	29.8
17	30.5
18	33.7
19	36.1
20	41.5
21	41.9
22	47.8
BODY BURDENS EXCEEDING THE 50.9 ED_{01}	
23	51.8
24	52.8
25	55.9
26	63.1
27	63.6
28	71.6
29	109.3
30	175.9

All concentrations in ppt.

> Additionally, because both Drs. Finley and Lyons have charged that my cancer risk estimates are unreasonable, I have calculated the cancer risks in the above table using the *maximum* ED_{01} of 50.9 ppt based on Ott and Zober 1996.

As shown in Exhibit 9, the range of total risks (including background risks) for the Facility cohort is 2.5 to 35 in-one-thousand (2.5E-3 to 3.5E-2). When the *average* background is subtracted for each worker to derive the individual Facility-related risk, the risks range from 0.046 to 7.7 in-one-thousand (4.6E-05 to 7.7E-03). This later cancer risk is the *average* site-related risk *only* associated with Facility dioxin and furan releases. Finally, after comparing the *site-related* cancer risk levels for each individual to EPA's acceptable risk level of 1E-4 (which was discussed in Dr. Finley's report), it can be concluded that 24 of the 30 workers have unacceptable cancer risk levels as a the direct result of their working tenure at the USM Facility. Accordingly, the critiques by Drs. Finley and Lyons that the only high risks are associated with the maximum exposed individual and only he has high risks do not apply.

Dr. Finley states:

> *In addition to issues associated with use of an ED01, there are also a number of scientific issues which have been raised relating to the three studies (Steenland et al. 2001; Becher et al. 1998; Ott and Zober 1996) used by USEPA to calculate the ED01 values that Dr. DeGrandchamp used in his analyses. The Steenland et al. 2001 study was utilized to characterize one end of the range and Ott and Zober 1996 was used to characterize the other. Examples of some of the limitations of these studies include:*

He then goes on to list sources of uncertainty in his report. I generally agree with most of his statements because there is always some uncertainty in science. However, Dr. Finley simply assumes that if we had more "facts" the uncertainty would always result in *lower* cancer risk estimates, and this is not the case. There has been much "uncertainty" introduced in cancer studies because of inappropriate comparisons to "non-exposed background cohorts." However, there is no such thing as a "non-exposed background cohort." All humans in industrialized countries have background levels of dioxins, and scientists now recognize that the differences in cancer rates that were observed in those studies may have been *underestimated* rather than overestimated.

In comparing cancer rates between exposed and non-exposed workers, the true comparison was really between low and high dioxin-exposed workers. This is comparable to comparing cancer rates for

light (or medium) and heavy smokers where the differences are compressed because cancers would develop in light smokers as well as heavy smokers. In such a comparison, the differences in cancer rates between the two groups will be compressed. Just as there is now reason to believe that diabetes may be associated with background levels of dioxin (which now nullifies the findings of many earlier studies), it may likewise be true that there is a background rate of cancer associated with background body burdens. A recent study by Steenland and Deddens (2007) indicates this may indeed be the case. They demonstrated a positive "exposure-response" relationship between dioxin and cancer rates, which is one key element in showing a causative link. Furthermore, the relationship was detected even though the "control" background was not truly a control population but a "dioxin-light population." This is just one example of the negative bias that has infused some past studies. Thus, Dr. Finley's interpretation of uncertainty and the bias it introduces does not mean the cancer risks would always be reduced.

I do recognize the uncertainty in all scientific studies; however, that does not mean the results are wrong. Scientists must use information based on the current state-of-the science, and what I have presented is just that. Unless Dr. Finley proposes an alternate source of well-designed studies showing cancer risks are not elevated in a comparison between a *true non-exposed* population and a dioxin-exposed cohort, we have little choice but to use the existing studies I find reasonable and credible. Instead, Dr. Finley simply states that there is uncertainty in the studies I use (which, incidentally have undergone extensive peer review) and that they are unreliable.

In section 4.3.3, Dr. Finley calculated risk associated with "Levels of Dioxin-Like Compounds in the General U.S. Population." These calculations are flawed, and he makes what scientists call "apples to oranges" comparisons, which are wrong. First, he states:

> *In this section, I provide an example of this for dioxin cancer risk. Specifically, the cancer risk associated with the body burden of dioxin-like compounds reported in NHANES was compared to the risk calculated for the NIOSH HHE cohort using the same methodology DeGrandchamp employed. The maximum value reported in Table 1a of Ferriby et al (2006) for the 17 PCDD/F congeners was 139.2 ppt (note this is the study DeGrandchamp selects as his reference population).*

This statement is incorrect for many reasons. First, it is factually incorrect, since the correct maximum value from the Ferriby *et al*. (2006) study is 94.9 ppt not 139.2 ppt. Second, the body burden he cites is

for women aged 60 years and older. There were no women in the Facility cohort workers nor were any of the workers in that age bracket. It is interesting to note that he is using the same Ferriby et al. (2006) study, which I used but which he stated was inappropriate. Third, Dr. Finley uses an inappropriate comparison by making unsupported assumptions about the maximum exposed individual in the background population. There is only one maximum exposed individual in the entire U.S. general public who has that level, and Dr. Finley simply assumes that person is not suffering from a dioxin-related medical condition such as diabetes, cancer, or some other health problem. Dr. Finley provides no medical information about that individual so it is an unsupported assumption. He equates background levels with "safe or health protective" levels, when recent evidence shows otherwise. As I have previously discussed, recent studies suggest diabetes may be occurring at background levels, and not at elevated background levels, but at average body burdens in the U.S general population. These levels are far below the "maximum" background in the U.S. general population.

The focus of my toxicological investigation of Facility workers can be simply stated: Are the site-related Facility worker exposures associated with unacceptable cancer risks? To answer this question, a two-step approach was developed. The first step is to quantify the increase in workers' dioxin-furan body burden above background as a result of their working tenure at USM. The only way to determine this is to subtract the background level from the current level for each worker. Dr. Finley seems to disagree with my approach of subtracting the average concentration from current levels for each worker, so I need to explain the concept I have followed (which, incidentally is generally accepted practice). We can never know the actual increase in *each individual* worker's dioxin level starting with his background level that he had on his first day of work. This is because blood samples are not taken from newly hired workers. However, when considered as an entire group of 30 and applying simple common sense, *if* we had the actual background level of dioxin for each of the 30 workers when they started work, their body burdens would have to mirror the average distribution of the background population simply because they were part of the U.S. general population before their employment. For example, a few would start their first day with dioxin levels below the background average, the majority would surround the average, and a few would be above the average. This is analogous to determining the average height for a population of citizens. If you measured a group of normal U.S. citizens, a few would be short, a majority would be of average height, and a few would be tall. But the calculated average in the experimental group would be close to the U.S. average calculated for the entire population. Similarly, individuals in the *group* of 30 Facility workers starting on day one would show the same distribution around the average, with a few having body burdens below average, the majority would be around the average, and a few would be

above average. It is reasonable to subtract the average body burden from each worker because, on *average,* this is the expected body burden.

Of course, it is possible I subtracted the average from someone with a starting body burden above average, but there is the same probability that I would do the same for someone starting with a body burden below the average. However, those errors would cancel each other for the whole group. This is why my approach for subtracting the average background from workers' current body burden is appropriate, and it provided information about individual variation within the Facility cohort.

Although the above approach is scientifically valid, I have calculated the *average* increase to address Dr. Finley's and Dr. Lyons's concern about undue emphasis on the maximum exposed individual.

The average increase in cancer risk for the Facility cohort can be calculated using the same equations Dr. Finley used. In this analysis, I used the maximum ED_{01} of 50.1 ppt to avoid overestimating risk (as I previously discussed). Using the same equations, the average background concentration of 19.0 ppt (Ferriby *et al.* 2006) is associated with a cancer risk of 3.8 in-one-thousand (3.8E-3). The average concentration of the Facility cohort is 41.5 ppt (based on WHO 2005) and is associated with risk of 8.2 in one thousand (or 8.2E-3). Thus the <u>average</u> cancer risk increases from 3.8E-3 to 8.2E-3, which represents a doubling of an *already* high background risk. Another way to calculate the increased average risk for workers is to subtract the *average* background from the *average* Facility cohort body burden, which is 22 ppt (22.3=41.5-19.0). This is the *average* increase in dioxins-furan body burden in Facility workers directly resulting from working at USM. This increased body burden of 22 ppt is associated with an <u>average increased cancer risk</u> of 1.1 in one thousand (1.1E-3). That is, the *average* cancer risk for the entire Facility cohort has *increased* by 1.1E-3. This second step of this two-step process yields the answer to the above question, confirming that the average site related increase for the Facility cohort is unacceptable. Moreover, this result confirms my alternate approach of subtracting the average background body burden from individual body burdens is correct. As shown in Exhibit 9, the average cancer risk was also 1.1E-3.

This site-related *increase* in risk of 1.1E-3 is an order of magnitude above the EPA acceptable risk level described by Dr. Finley in his human health risk assessment. The only conclusion that can be drawn is that the *average increased* risk for the entire group is far above acceptable levels and not just in the maximum exposed individual, as suggested by Drs. Finley and Lyons.

Dr. Finley states:

> *In an attempt to quantify noncancer risk, DeGrandchamp used the measured maximum body burden from the NIOSH HHE cohort, subtracted background levels (as he did in the cancer risk calculations), and converted the resulting body burden level to an average daily dose (ADD) which relies on assumptions relating to half life and absorption (DeGrandchamp, Exhibit 6).*

He then states:

> *Given that the maximum TEQ body burden observed in the general population is higher than the maximum TEQ body burden in the NIOSH HHE cohort, the estimated non-cancer risk for the highest-observed body burden in the general population would be higher than that calculated for the maximum person in the NIOSH HHE cohort. The WHO TDI of 1 to 4 pg/kg-day is a conservative and protective value for all.*

As I stated previously, this statement is factually incorrect. The body burden of the maximum exposed worker is much higher than the maximum in the background. As I also previously discussed, background is not synonymous with safe levels.

Dr. Finley states:

> *Calculation of an average daily dose based on a known body burden requires an input value for half-life. Dr. DeGrandchamp uses a value of 7.5 years, though a citation for this value was not provided. Given that the elimination kinetics of dioxin are concentration and age dependent (Aylward et al 2005), Dr. DeGrandchamp should have, at a minimum, noted the use of a generic value for half- life as a point of uncertainty in his assessment. In addition, DeGrandchamp is using an input body burden based on TEQ whereas the default half- life value is based on TCDD alone. It is well documented that the half-lives for the other congeners which comprise the TEQ are highly variable (Lorber et al 2002).*

I evaluated the dose-dependent elimination of dioxins as described by Aylward *et al.* (2005), as well as others, before I determined the half-life of 7.5 years is the correct value. As Dr. Finley points out, this phenomenon is important, and it appears to be supported by Geusau *et al.* (2001) in their clinical studies of two women who were severally poisoned. They had body burdens of dioxins in the tens of thousands

ppt and eliminated dioxins with a much shorter half-life than 7.5 (i.e., they eliminated it several times faster). The dose-dependent phenomenon can be described by the following analogy. If a very tall cylinder is filled with water and a hole is punctured on the bottom, the rate at which the water pours out the hole is dependent on the pressure or the height of the water. At the beginning, the water pours out fast, but it slows to a trickle as the water level approaches the level of the hole. Likewise, it is theorized that dioxin is eliminated from the body at a very fast rate when body burdens are in the thousands of ppt. However, as the body burden decreases, the elimination rate is reduced and the half-life is shown to be about 7-7.5. Since the Facility workers have body burdens 2-7 times background, rather than in the thousands of ppt, the half-life of 7.5 is correct and appropriate for the Facility cohort.

Dr. Finley states:

> *While it is a minor point, it is also of interest to note that, as written, DeGrandchamp does not account for the conversion of body burden (given in ppt, or pg/g) to pg/kg for the daily dose (pg/kg-day). The resulting daily dose calculated by DeGrandchamp incorporates this conversion, but Dr. DeGrandchamp has either left it out in error or has simply not been transparent with his calculations.*

The equation and results are correct. However, Dr. Finley is correct the conversion was not explicitly stated. I simply made the conversion within the calculation by multiplying by 1,000 in my head.

Dr. Finley states:

> *The WHO TDI of 1 to 4 pg/kg-day is a conservative and protective value for all effects of dioxin-like compounds – cancer and non-cancer.*

I agree this is a health protective exposure level. The problem is that the Facility workers are already exposed to this safe TDI as part of their *background* exposures. Therefore, any additional exposure from the Facility poses noncancer health hazards. Furthermore, subtle toxic effects may be occurring even *at* background exposures in the U.S. general population (EPA 2003):

> *Although past EPA risk assessments have focused on cancer estimates based on extrapolation models as the major concern for dioxin and related compounds, more recent data suggest that*

> *noncancer effects may be occurring at or near human background steady-state body burden levels in animals and in humans.*

Dr. Finley misstates the conclusions of the WHO, which are:

> *The consultation therefore stressed that the upper range of the TDI of 4 pg TEQ/kg bw should be considered a maximal tolerable intake on a provisional basis and that the ultimate goal is to reduce human intake levels below 1 pg TEQ/kg bw/day.*

That is, the TDI of 4 pg/kg-day is not a safe daily level. Rather, it represents a ceiling that should not be *exceeded*. Unlike cancer risks where there is continuous spectrum of risks, the noncancer TDI is a bright line that should not be exceeded. What I attempted to convey was that if Facility-exposures alone are 16 times higher (excluding background) than the TDI, it would present a health concern. The TDI is identical to the RfD, which Dr. Finley discussed in his HHRA. As he concluded an RfD that exceeds 1.0 may pose unacceptable health hazards. Likewise, an exposure 16 times the maximum safe exposure represented by the TDI is of considerable concern. Furthermore, the TDI represents the total dioxin TEQ from both background and site-specific dioxins, furans, and PCBs exposures. My calculations did not take into account non-Facility related exposures because I assumed that would be obvious. Since it is not, I calculated the total dioxin TEQ based on the total body burden of dioxins and furans in Facility employees (NIOSH 2005) and added their DL-PCB body burdens that I have already shown are at background levels. To be consistent with the WHO-derived TDI, I used the WHO-1998 TEFs for my calculations of the average and maximum intake rates of 20 and 78 pg/kg-day, respectively. Consequently, based on total dioxin TEQ exposure, the average and maximum Facility worker is exposed to 5 and 19 times the maximum of 4 pg/kg-day TDI which is a health-based bright line.

Dr. Finley states:

> *Based on a quote from the WHO relating to the proposed TDI, Dr. DeGrandchamp stated that "subtle toxic effects may be occurring at background levels. Therefore, any exposure added to background exposures will certainly have some toxic effect," (p. 32). In drawing this association, DeGrandchamp has clearly not considered that the overall weight of the scientific evidence does not support an association between exposures to background levels of dioxin-like compounds and the occurrence of adverse health effects in humans.*

I have considered the weight of evidence. I have concluded there is now much stronger evidence for high cancer risk as well as non-cancer effects, such as diabetes.

Dr. Finley quotes EPA (2003), stating:

> *"Clearly adverse effects, including, perhaps, cancer, may not be detectable until exposures contribute to body burdens that exceed current background by one or two order of magnitude (10 to 100 times), (USEPA 2003, p. 6-2)."*

What Dr. Finley doesn't state is why EPA made this statement. The operable word is "detectable" and that means that the difference between a dioxin-exposed group and a non-dioxin-exposed group has to be sufficiently large to "detect" it. As I have repeatedly stated, since past studies have actually measured differences between "light dioxin-exposed groups" and "heavy dioxin-exposed groups," the differences would be artificially compressed. The only way to "detect" a difference at background levels is to find a truly non-exposed population, which doesn't exist. The above statement can in no way be interpreted as meaning that cancer is not produced at background levels, because EPA states repeatedly in many documents that the cancer rate is elevated even at background levels.

Dr. Finley states:

> *Furthermore, there are no well-defined exposure-response relationships for dioxin-like compounds; particularly for exposure at background levels. A variety of health effects have been examined in numerous epidemiological studies of highly exposed populations over the past several decades.*

This statement is incorrect. While it is true that numerous epidemiological studies have examined dioxin, it is now recognized that they all suffered from a lack of statistical power or robustness. This is because non-dioxin exposed populations do not exist. In more recent studies, unique scientific approaches have been applied. In these studies, scientists have focused on individual dioxin congeners instead of total dioxin TEQ. They have identified some individuals in the background population that do not have any detectable levels of specific individual congeners enabling a comparison to truly non-dioxin (congener) exposed groups. In these studies, Lee et al have demonstrated dramatic dose-response relationships between diabetes and individual dioxin congeners at average background levels.

4.3 Dioxin Cancer Classification

Dr. Finley states:

> *First, investigators have classified TCDD as one of the most toxic chemicals, based primarily on the very low LD50's observed in guinea pigs, the most sensitive of all species tested. This is the basis for Dr. DeGrandchamp's statement that dioxin is "the most potent carcinogen EPA has ever studied." This statement is not based on actual human data.*

What I actually stated in my report (pg. 9) was, *"Although the cancer potency of dioxin is still under investigation, the provisional cancer potency factor (which describes the ability of dioxin to produce a tumor) is the highest of any chemical EPA has evaluated. Dioxin has been shown to produce cancer at far lower concentrations than any of the more than 600 other chemicals EPA has studied and for which EPA has developed cancer potency values. Not only is dioxin the most potent carcinogen EPA has ever studied, but the current cancer potency of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, the parent congener for the family of dioxins discussed below) is approximately 100 times greater than the second-most carcinogenic chemical (diethylstilbestrol) and 1000 times more carcinogenic than the third-most carcinogenic (benzidine)."*

My original statement stands correct and has nothing to do with either the LD50 or guinea pigs. Simply put, dioxin is by far the most potent carcinogen EPA has ever studied. However, it is noteworthy that the very first sentence in the Preface of the NAS dioxin review, which Dr. Finley cites and quotes throughout his expert report, is as follows:

> "*2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), also called dioxin, is among the most toxic anthropogenic substances ever identified."*

Notwithstanding Dr. Finley's mischaracterization of my statement, I do agree with Dr. Finley that there is considerable variation among different species experimentally exposed to dioxin. That is precisely why I relied on the results from *human* studies to determine the carcinogenic risk to Facility workers. The NAS (2006) review suggested EPA investigate "Other Toxic End Points" because they concluded those other toxic endpoints are as significant as cancer. NAS (2006) states:

> *Although TCDD, other dioxins, and DLCs* [dioxin-like compounds] *have received wide recognition for their potential to cause cancer, birth defects, reproductive disorders, immunotoxicity, and chloracne, animal* ***and human studies*** [emphasis added] *have demonstrated other potential toxic end points, including liver disease, thyroid dysfunction, lipid disorders, neurotoxicity, cardiovascular disease, and metabolic disorders, such as diabetes.*

4.4 Dioxin Noncancer Health Hazard

In addition to high cancer risks, I conducted a careful toxicological analysis of potential noncancer health effects associated with elevated dioxin body burdens in Facility workers. The diabetes prevalence rate in the Facility cohort is 17%, which is 2.5 times the background prevalence rate of 6.7% in Utah men aged 40-59. The increase could be related to their exposure to dioxin and HCB at the Facility.

4.4.1 Diabetes

4.4.1.1 Diabetes Prevalence in Facility Workers is Very High

I have calculated a diabetes prevalence rate in Facility workers that is 17%. This rate is much higher than the Utah background rate of 6.7% in men aged 40-59. Based on a careful review of recent peer-review studies that show a "strong" link between diabetes and dioxins even at *background* levels, it may be possible the increase in diabetes prevalence may be associated with the workers' high dioxin and HCB body burdens.

The new findings linking dioxin and diabetes are in stark contrast to Dr. Finley's position that there is no association. To evaluate the veracity of his position and his critique of my report regarding this issue, I felt it was important to take a closer look at the actual diabetes prevalence rate in the Facility cohort. I conducted this reevaluation in tandem with an evaluation of several very important and provocative studies that now show a "strong" correlation between dioxin body burdens and diabetes prevalence rates (Lee *et al.* 2006 and 2007; and Everett *et al.* 2007; Kang *et al.* 2006; Rylander *et al.* 2005; Fierens *et al.* 2003; and Cranmer *et al.* 2000). In addition, I reviewed evidence-linking diabetes with HCB body burdens, and I concluded that dioxin and HCB could be acting in concert in the Facility workers to produce the very high diabetes prevalence rate.

In the analysis of Facility workers, I first determined the number of workers in the Facility cohort who reported having diabetes in the NIOSH (2005) study. Table 4 in the NIOSH study shows that 5 of the 30 workers (17%) in the Facility cohort who participated in the study reported having diabetes.

The next step was to compare the Facility cohort prevalence rate to age-adjusted background rates for men living in Utah. The Utah Department of Health (UDH) maintains up-to-date health statistics on Utah residents on its database, the Indicator Based Information System for Public Health (IBIS-PH). The IBIS database is used to track the health status of Utah residents, which include rates of diabetes in the general population. IBIS was queried to determine the percentage of Utah males aged 40 to 59 who had diabetes (2,531 individuals) for the years 2004 to 2006. For this period, the background age-adjusted prevalence rate of diabetes was 6.7% (CI: 5.5%-8.1%).

Comparing the actual Facility cohort and background diabetes rates reveals the workers have a significantly elevated diabetes prevalence rate much higher than expected. Based on the high rate of diabetes within the Facility cohort, I conducted a thorough evaluation of all pertinent recent studies. I have concluded the high prevalence of diabetes in the cohort may be a direct result of the Facility-related exposures.

4.4.1.2 Recent Studies Show Strong Dioxin-Diabetes Association

Dr.Finley concluded there is no association between dioxin and diabetes simply based on reading the NAS (2001) report. However, he did not discuss the much more recent and relevant studies (the studies cited in the NAS report are now outdated). These new studies were designed specifically to eliminate flaws that are inherent in most of the historical diabetes studies Dr. Finley references. Before I discuss the new findings, I need to explain why—according to Dr. Finley—some controversy has existed.

The scientific approaches employed in early studies were flawed and unintentionally produced biased results where the dioxin-diabetes link was obscured. It is now well recognized that these flaws prevented scientists from distinguishing any differences in diabetes prevalence rates between a dioxin-exposed group and a "non-dioxin exposed" control group. Even 6 years ago, the NAS (2001) report (upon which Dr. Finley based most of his conclusions) identified some of these "potential" flaws. NAS suggested that researchers may not have been able to identify a dioxin-diabetes link because they measured the rate of *mortality* (number of deaths) from diabetes rather than *morbidity* (number of diagnosed diabetics). That is, instead of determining the actual diabetes prevalence rate in a population, the researchers simply reviewed death certificates to determine whether the cause of death was diabetes. In hindsight, the

problem with this approach is clear: diabetes is only rarely listed as the cause of death. Instead, the actual listed cause of death is usually a secondary complication *from* diabetes, making it impossible to identify who had diabetes solely from their death certificates. Although some studies were able to detect a positive association, NAS (2001) considered this scientific approach to be flawed, stating:

> *Positive associations are reported in many mortality studies, which may underestimate the incidence of diabetes. Morbidity (the rate of incidence of a disease) is thought to be a more informative end point than mortality (the rate of death) when conducting epidemiologic studies of Type 2 diabetes because the disease is not typically fatal, its known complications may be more likely to be implicated as the underlying cause of death, and reporting of contributory causes of death on death certificates may be spotty.*

However, NAS (2001) also noted that some researchers explained that they did not think underreporting was significant:

> *These reasons also lead epidemiologists to suspect that mortality studies may underestimate the incidence of diabetes, although, as Steenland and colleagues (1992) point out, such underreporting might be expected to equally affect the exposed and referent populations and thus wash out the effect.*

This is an inadequate and incorrect explanation: reducing the number of confirmed diabetics in both dioxin- and "non-dioxin" exposed groups still leads to artificially low prevalence rates. Although Steenland and colleagues (1992) are correct that underreporting diabetes from death certificates would equally affect both exposed and control populations, what they fail to note is that the net effect would *not* be a zero-sum result. This is because the "magnitude" of the population difference is critical. That is, it is necessary to detect a large enough difference between two populations—which scientists call a "statistically significant difference"—in order to detect a link between dioxin exposure and diabetes. By reducing the number of diabetes cases in both exposed and control groups, the difference between the groups is too small to detect. Since diabetes as the cause of death is artificially low in *both* populations, any difference between the two groups would be too small and would be statistically undetectable.

Remillard and Bunce (2002) discuss this flaw in their detailed review of past diabetes mortality studies in *Linking Dioxins to Diabetes: Epidemiology and Biologic Plausibility* and provide a common sense analogy of this study design flaw. They suggest that it would be similar to scientists determining if there

is a link between cigarette smoking and cancer by comparing rates of lung cancer between heavy smokers and light smokers rather than between heavy smokers and nonsmokers. Obviously, the statistical difference in cancer rates between heavy smokers and light smokers will be compressed. This is because both groups will have elevated rates of cancer. A much greater difference in cancer rate would be observed between heavy smokers and *nonsmokers*. Importantly, they also identify another point of "compression" that involves the so-called "non-dioxin exposed" control group. The fact is that there is no such group. All U.S. citizens (as well as people living in other industrialized countries) are exposed to background sources of dioxin on a daily basis (primarily in our diets), so everyone has a background dioxin body burden. Using the above analogy, comparing dioxin-exposed and "non-dioxin exposed" control groups much more correctly describes a comparison between "heavy" dioxin exposure and "light" dioxin exposure. Remillard and Bunce (2002) correctly note that at the time of their review, it was unknown whether background levels of dioxin could be associated with diabetes:

> *In addition, present knowledge does not indicate the significance of chronic exposure to approximately 5 pg TCDD/g serum lipid (or 35 pg TEQ per gram of serum lipid) in the general population.*

The above-discussed experimental flaws explain why, according to Dr. Finley, there have been inconsistent findings in dioxin-diabetes studies.

In one of the most recent studies conducted by Lee *et al.* (2006), the researchers measured the rate of morbidity (prevalence of diagnosed diabetes) rather than mortality. In their study, they identified a "true" control group that had zero body-burdens for specific individual congeners to avoid the comparison of "heavy dioxin" and "light dioxin" body burdens. Evaluating the link between diabetes prevalence rates and body burdens in the U.S. general population (1999-2002 NHANES), they were able to show for the first time that not only is there is a link between dioxin and diabetes, but that a "strong" dose-response relationship exists. What made this study unique and groundbreaking is that diabetes was studied in a "true" non-dioxin exposed population for the first time. As I discussed, they accomplished this by focusing on individual dioxin congeners instead of total dioxin TEQ. Indeed, Lee *et al.* suggests this is why they were able to detect a "strong" dose-response relationship where earlier investigators had failed.

> *Dose-response relations shown in this study were surprisingly strong compared with the weak to modest associations shown in the previous epidemiological studies. Our study had two important design features lacking in other* **[earlier mortality studies]**: *first, we selected those POPs*

> [persistant organic pollutants] *for which we were sure those with non-detectable levels would have very low levels and could serve as the reference* **[control group]** *group; and second, we evaluated a composite of POP levels. In our study, the risk of prevalent diabetes increased consistently across the range of SUMPOPs* [sum of persistent organic pollutants]. *In this situation, the selection of the reference group is statistically critical to the estimated strength of ORs* [odds ratios]. *For example, if we pooled the lower four categories of POPs as the referent group and compared it with the highest category, the OR would be substantially underestimated. In fact, most previous epidemiological studies on POPs were performed with subjects who had exposure to higher concentrations of POPs in occupational or accidental settings taking the general population as the reference group. However, our current result suggests that this kind of approach may not be valid because* ***there may be a much clearer dose-response relation in the lower concentrations of background concentrations of POPs in the general population*** [emphasis added].

In other words, by focusing on individual dioxin congeners (individual dioxin compounds) rather than total dioxin TEQ, they identified a segment of the U.S population in which body burdens for 6 compounds were zero (not detected). Included in this group of 6 were HpCDD and OCDD. Even after correcting for age, sex, race/ethnicity, poverty income ratio, BMI, and waist circumference, the correlations were still "strong." They also found that evaluating confounders such as triglyceride, cholesterol, saturated, fat intake, and cigarette smoking did not "materially change the results."

I present a summary of the findings of Lee *et al.* (2006) in Exhibit 12 to demonstrate just how strong the dioxin-diabetes correlation is for both HpCDD and OCDD. As can be seen, the diabetes prevalence rate steadily increases with progressively higher body burdens of HpCDD. For example, I have highlighted the row showing diabetes prevalence increases from 4.4% for a body burden of 20.7 ppt HpCDD (which is the 25th percentile in the U.S. general population) to 26% with a body burden of 170 ppt. The same dose-response incremental increase is seen for OCDD. These findings are very important because, for the first time, there is evidence that diabetes may be associated with dioxin at very low background levels. This concept is also important because Dr. Finley repeatedly equates "background body burden" with "safe" levels. Moreover, these results are directly relevant and applicable to my toxicological analysis of the Facility cohort because the diabetic effects Lee *et al.* describe are even *below* the average body burden of these 2 dioxin-like congeners in the Facility cohort. For example, Lee *et al.* shows a diabetes-dioxin effect as low as 38 ppt HpCDD body burden, while the *average* body burden in the Facility cohort was 36 ppt and the maximum was 83 ppt. Similarly, they showed an effect level for OCDD at 194 ppt, while the

average and maximum for the Facility cohort was 282 ppt and 1060 ppt. In summary, Lee *et al.* have shown a diabetes-dioxin link at levels even below the *average* levels in the Facility workers.

EXHIBIT 12: LEE *ET AL.* (2006): STRONG DIOXIN-DIABETES CORRELATION IN U.S. BACKGROUND POPULATION

CHARACTERISTIC	BODY BURDEN-PERCENTILE IN NHANES					
	NOT DETECTABLE	**<25th**	**25th-<50th**	**50th-<75th**	**75th-<90th**	**90th and Over**
Dioxin-HPCDD						
Body Burden (ppt)		20.7	37.8	60.8	97.5	170
Diabetics (Total Participants)	12 (263)	19 (436)	44 (439)	56 (439)	40 (262)	46 (177)
Diabetes Prevalence (%)	**4.6**	**4.4**	**10.0**	**12.8**	**15.3**	**26.0**
Adjusted Odds Ratio	Control	1.0	1.7	1.8	1.6	2.7
OCDD						
Body Burden (ppt)		194	323	514	805	1,485
Diabetes (Total Participants)	13 (390)	30 (401)	47 (410)	46 (408)	50 (241)	31 (166)
Diabetes Prevalence (%)	3.3	7.5	11.5	11.3	20.8	18.7
Adjusted Odds Ratio	Control	1.7	2.2	1.6	2.7	2.1

Body Burden: Lipid adjusted serum ppt.

The fact that diabetes may be associated with lower concentrations of dioxins is also a new finding that may explain why earlier studies did not find a "strong" link. According to Lee *et al.* (2006):

> *Humans are currently regarded as a less-susceptible species with respect to TCDD or other congeners based on findings of previous epidemiological studies with subjects having high exposure to POPs. However, the chronic exposure to low concentrations of POPs in the general population may be more detrimental in developing adverse health effects than previously thought.*

> *Along these lines, it is worthwhile to note that the most consistent dose-response associations between POPs and diabetes appeared to occur in epidemiological studies with subjects having lower serum concentrations of TCDD than in occupational settings (4,8), conceivably because of the statistical artifact of not identifying a true low-risk subgroup. Unlike prior studies, in this study, we analyzed several POPs simultaneously so that we could estimate the cumulative effect of exposure mixtures. In most previous studies, only serum concentrations of TCDD were measured. Although TCDD is well known to be the most potent POP because of a strong affinity to AhR* [Ah Receptor; biological target molecule for dioxin-like effects]*, other mechanisms might also be involved in the toxicity of POPs for diabetes (39). Thus, other POPs, as well as TCDD, might be relevant in the pathogenesis of diabetes.*

Other studies—including a follow up study by Lee *et al.* (2007)—have confirmed and extended the initial Lee *et al.* findings. Collectively, these new studies provide compelling evidence.

Lee *et al.* (2007) published an extended analysis of their 2006 study by increasing the number of dioxin-like chemicals analyzed. Their earlier results were confirmed, showing once again that dioxins and furans are linked to an increase in prevalence of diabetes in a dose-dependent manner. However, they also noted there were differences in the prevalence rate between the 6 classes of contaminants and between individual dioxin congeners. That is, some dioxin and furan congeners were stronger than others (and two tested were not associated with diabetes). They concluded:

> *In separate models of each POP individually, most POPs belonging to all 5 sub-classes of POPs were positively associated with the prevalence of diabetes, but differed substantially across POP subclasses. Specific PCDDs or PCDFs were weakly associated with diabetes while POPs belonging to PCBs or OC pesticides were strongly associated.*

Everett *et al.* (2007) confirmed both Lee *et al.* studies. They used the NHANES data in a similar experimental design, but extended the Lee *et al.* (2006) investigation to include undiagnosed diabetes as well as diagnosed diabetes. Everett *et al.* evaluated PCB 126, p,p-DDT, and 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin (HxCDD), and found that all *"…three compounds were significantly associated with diagnosed diabetes."* Their results add considerable weight to the two Lee *et al.* studies.

Kang *et al.* (2006) provide additional support for the link between dioxin and diabetes exposure. They found a significantly higher risk of diabetes (among other medical conditions) among those personnel

who sprayed Agent Orange in Vietnam (similar to the Air Force Ranch Hand group) compared to Vietnam veterans who did not spray Agent Orange.

Rylander *et al.* (2005) investigated the incidence of diabetes in Swedish fishermen and their wives whose diets were high in fatty fish. They measured the serum levels of PCB-153 (a dioxin-like PCB) and DDE (the main by-product of DDT) and found those with diabetes to have significantly higher blood levels of both contaminants than did non-diabetics. Fierens *et al.* (2003) conducted a study in Belgium on 257 (142 women and 115 men) and found diabetics had 62% higher serum levels of dioxins. Cranmer *et al.* (2000) investigated a population of residents living near the Vertac/Hercules facility, a Superfund site in Jacksonville, Arkansas, that manufactured Agent Orange. The researchers found widespread and persistent TCDD contamination of local streams, parks, and yards surrounding the facility. Diabetes prevalence rates were higher in those with higher blood TCDD levels. The researchers concluded their findings could not be explained by other known risk factors.

4.4.1.3 A Review of Historical Diabetes Studies

In reviewing earlier studies, there were positive associations in studies noted in the NAS (2001) report Dr. Finley cites. Roegner (1991) found that veterans with blood dioxin greater than 33.3 pg/g have a relative risk of 2.5 for diabetes. Henriksen *et al.* (1997) found that veterans exposed to dioxin had a higher risk of developing diabetes and that veterans exposed to dioxin develop diabetes earlier than other veterans.

The association between dioxin and diabetes was noted in the NIOSH cohort and reports of an increase in diabetes in the Ranch Hand cohort (Michalek *et al.* 1999a; Longnecker and Michalek 2000) were also published. There was not a significant increase in diabetes in the NIOSH study based on mortality, although six of the 10 most highly exposed workers did have diabetes. However, as previously discussed, mortality studies are limited in power to detect differences in diabetes. Longnecker and Michalek (2000) found a pattern suggesting that low levels of dioxin may influence the prevalence of diabetes. However, a clear dose response was lacking. A more recent update of the Ranch Hand study, however, shows a 47% excess of diabetes in the most heavily exposed group of veterans (Michalek *et al.* 1999). Dioxins may produce higher risks of diabetes in individuals at younger ages.

4.4.1.4 There May Be a Link Between HCB and Diabetes

Although there are fewer recent studies on HCB-related diabetes (probably because it has not been manufactured or used in the last 30 years) than on dioxins, some recent studies have suggested that HCB

may also be associated with diabetes. Radikova1 *et al.* (2004) investigated diabetes in a total of 2050 adults in Slovakia (835 males 1215 females) and found that HCB, among other organochlorine compounds, was "predictive" for diabetes. Likewise, Glynn *et al.* (2003) showed that Swedish women with the highest body burdens of HCB had a unique relationship with diabetes, showing the highest statistical relevance compared with PCBs. Exhibit 13 shows that of all the organochlorines they tested, HCB had the strongest statistical relationship as indicated by the *lowest p*-value level shown in the last column.

EXHIBIT 13: GLYNN *ET AL.* (2003) DIABETES RESULTS

Table 5. Organochlorine concentrations in women with or without diabetes.[a]

Compound	Diabetes (n = 7) (ng/g lipid)	No diabetes (n = 198) (ng/g lipid)	p-Value[b]
PCB 105	8 (5–12)	5 (5–6)	0.07
PCB 118	58 (40–84)	40 (38–43)	0.06
PCB 138	115 (82–160)	98 (92–104)	0.35
PCB 153	251 (190–330)	219 (208–230)	0.33
PCB 156	20 (16–26)	18 (17–19)	0.32
PCB 167	11 (8–16)	8 (8–9)	0.10
PCB 180	171 (135–215)	153 (146–160)	0.35
p,p'-DDE	602 (331–1,095)	464 (415–519)	0.39
HCB	85 (66–109)	60 (58–63)	0.008
β-HCH	64 (44–94)	49 (45–52)	0.16
trans-Nonachlor	29 (21–40)	23 (21–24)	0.12
Oxychlordane	17 (12–23)	13 (12–14)	0.12

[a]Adjusted geometric mean (95% confidence interval); results adjusted for region, age, BMI, and weight change; diabetes type not specified. [b]Significance levels represent the overall test of differences in geometrical means.

4.4.1.5 Older Diabetes Studies

Dr. Finley (pg. 8) identified a typographical error in my report regarding the link between dioxin and diabetes. He states:

> *However, Dr. DeGrandchamp states that there is "strong evidence of an association between exposure to dioxin and Type 2 diabetes," based on the 2001 IOM report...Given these statements, it is difficult to understand how Dr. DeGrandchamp has classified the association between dioxin exposure and Type 2 diabetes as "strong" when the IOM has repeatedly classified the association as "limited/suggestive."*

First, the NAS (2001) report is outdated, and some findings are no longer relevant because more recent published studies now confirm there is indeed a "strong" link between dioxin and diabetes. Secondly, what I actually wrote (pg. 16) was:

> *In its updated report, the National Academy of Sciences (NAS), Institute of Medicine (NAS 2001), concluded that there is strong evidence of an association between exposure to dioxin and Type 2 diabetes.*

The word "strong" was a typographical error and the word should have been "stronger." Prior to the latest 2001 NAS report, there were 2 prior NAS reviews titled: *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam; Veterans and Agent Orange and Update 1996* and *Veterans and Agent Orange: Update 1998.* I used the word "stronger" to convey that the fact that with each updated report, evidence linking dioxin exposure and diabetes is getting much stronger, *not* weaker. NAS (2001) indicates this in their statement:

> *Based on the scientific evidence reviewed in this report as well as the cumulative findings of research reviewed in the previous Veterans and Agent Orange reports, the committee finds that there is limited/suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant dioxin and Type 2 diabetes.* ***This is a change in classification from previous Veterans and Agent Orange reports, which found inadequate/insufficient evidence to determine whether an association existed*** [emphasis added].

After reviewing the most recent studies showing a "strong" dose-response relationship between dioxin and diabetes, I am confident the next NAS review will conclude there is unequivocal evidence of a clear link.

The NAS (2001) report based its upgraded classification on the following:

> *Positive associations are reported in most of the morbidity studies identified by the committee. Several studies that used Type 2 diabetes morbidity as an outcome measure have been published since the last Veterans and Agent Orange review: studies of male and female Vietnam veterans from Australia; a National Institute for Occupational Safety and Health (NIOSH) study of U.S. chemical workers; the Air Force Health Study (Ranch Hand study); and a separate examination of the Ranch Hand comparison group. Although some of the risk estimates in the studies*

> *examined by the committee are not statistically significant and, individually, studies can be faulted for various methodological reasons, the accumulation of positive evidence is suggestive.*

Is should also be noted that, as a result of the updated classification of the NAS studies, the Veterans Administration (VA) on July 9, 2001 added diabetes mellitus (Type II, adult onset) as a presumptive condition for in-country Vietnam veterans. In effect, the VA concluded sufficient evidence of a cause and effect relationship between dioxin (Agent Orange) and diabetes exists, and the VA started providing medical benefits to exposed Vietnam veterans.

4.4.2 Immunotoxicity

Dr. Finley (pg. 8) suggests I have not fully considered the weight of evidence relating to immunotoxicity. He states:

> *However, while he cites selected studies, he fails to consider the overall weight of the evidence as done by the NAS panel charged with reviewing the USEPA Dioxin Reassessment. In their review, the NAS panel concluded that "Present clinical findings are inconclusive about whether or in what way DLCs are immunotoxic in humans, a conclusion that EPA acknowledges, and human data are also sparse. Perhaps the most compelling data that DLCs are human immunotoxicants, at possibly relevant environmental levels, come from the studies of the Dutch children's cohort. These studies show an association between prenatal exposure to DLCs and changes in immune status. However, the effects are modest and do not lie significantly outside the full range of normal."*

While this is a portion of the NAS statements regarding dioxin-induced immunotoxicity, it does not fully characterize the entire NAS review with regard to dioxin-induced immunotoxicity. Additionally, the quote he selects does not address the core issue of the importance of immunotoxicity as it relates to cancer that I attempted to highlight in my expert report. Although the immune system is responsible for fighting infections and disease, it is equally responsible for destroying nascent transformed (cancer) cells before they can fully develop into cancerous tumors. That is, when we are exposed to a cancer-causing chemical and the chemical causes a normal cell to undergo a transformation to a cancer cell, the immune system recognizes the transformed cell as "foreign" and destroys it. This scenario is played out many times each day as the immune system routinely kills transformed cells before they can develop into a tumor (a mass of transformed cancer cells); this process is termed "immunosurveillance." The Dutch children's cohort

mentioned by Dr. Finley did not measure or investigate the relationship between dioxin-induced immunotoxicity and cancer. It simply measured the overall health of the children's immune systems. The concern I expressed in my expert report was that dioxin-induced immunotoxicity could compromise the immune systems of Facility workers and predispose them to cancer. NAS (2006) noted:

> *TCDD, other dioxins, and DLCs have well-known effects on the immune systems of experimental animals. Chemically induced alterations in immune function could result in various adverse health outcomes because the immune system plays a critical role in fighting off infections, killing cancer cells at early stages, and implementing numerous other health-protective functions. In light of the large database showing that TCDD, other dioxins, and DLCs produce immunotoxic responses in laboratory animal studies, combined with sparse human data, the committee agrees with EPA's conclusion that these compounds are probably human immunotoxicants.*

In addition to the NAS report, ATSDR has concluded that dioxins produce immunotoxicity. Indeed, unlike EPA, ATSDR has formally developed a toxicity value for noncancer effects associated with dioxin, and the toxic endpoint is immunotoxicity. That is, ATSDR has not only concluded that dioxins produce immunotoxicity, but that immunotoxic effects are among the earliest and most sensitive toxic effects.

Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Section 104(3) (Superfund), the Agency for Toxic Substances and Disease Registry (ATSDR) is mandated to address the potential health impact of hazardous substances to human health at Superfund sites. For each chemical that is routinely detected at Superfund sites, ATSDR is responsible for developing a chemical specific "Toxicological Profile," which presents a wealth of toxicological information, as well as health-protective exposure levels. The noncancer toxicity values ATSDR has developed to ensure people will not be harmed by contaminant exposures are termed "minimal risk levels" (MRLs). MRLs are defined as specific levels of contaminant exposure that will pose minimal risk of adverse, noncancer health effects for a specified exposure period. ATSDR has derived MRLs so that when a hazardous waste site is cleaned up to levels corresponding to MRLs, the site will pose no health hazards. It should be stressed that the derivation and toxicological interpretation of an ATSDR-derived MRL is identical to that for EPA's "reference dose" (RfD), which I discussed in my earlier report. As I explained, the derivation of either an MRL or RfD is a two-step process. The first step is identifying the target organ that is most sensitive to a particular toxic chemical and the toxic effect in that organ, while the second step involves determining the lowest effective dose or exposure that produces that particular

toxic effect. ATSDR follows this two-step process in its toxicological assessment of the approximately 275 chemicals most frequently detected at Superfund sites. According to a recent review of ATSDR-derived MRLs, Abadin *et al.* (2007) found that, of the 346 MRLs derived by ATSDR, immunotoxicity was identified as the most sensitive toxic effect for *only* 15 chemicals. This select group includes two dioxin-like compounds: 2,3,4,7,8-pentachlorodibenzofuran and (TCDD).

Exhibit 14 summarizes the ATSDR-derived MRLs based on immunotoxicity for these dioxins.

EXHIBIT 14: MRLS FOR DIOXINS BASED ON IMMUNOTOXICITY

CHEMICAL	EXPOSURE DURATION	MRL (mg/kg-day)	MOST SENSITIVE TOXIC EFFECT
2,3,4,7,8 Pentachlorodibenzofuran	Acute	0.000001	Mild, thymic lymphoid hypoplasia
2,3,7,8-TCDD	Acute	0.0000002	Decreased resistance to influenza virus
2,3,7,8-TCDD	Intermediate	0.00000002	Decreased thymus weights

Abadin *et al.* (2006) state the following regarding the reason that ATSDR considers immunotoxicity so important:

> *The role of the immune system is to provide immunity, that is, to maintain the homeostatic condition required by the body to protect it from disease (Burns-Naas et al., 2001). Immunotoxicity refers to any condition, which perturbs this homeostasis. Chemically induced effects on the immune system can result in (a) immunosuppression, potentially decreasing resistance to infection or cancer, (b) enhanced immunity, or (c) dysregulation of the immune response, potentially leading to autoimmunity or hypersensitivity.*

4.5 Highly Sensitive Individuals and Dioxin in Food

4.5.1 Take Home Contamination Exposes Sensitive Receptors

Dr. Finley states that fetuses and newborns are exposed to dioxins and furans but that these are simply background exposures. It should be noted that I was specifically referring to take home contamination. Exposure could result from take home contamination by either male or female employees from contaminated clothing or bodies, or it could occur from female employees breastfeeding.

It is a fundamental toxicological principle that children are more sensitive on a body weight basis compared to adults. For most chemicals, and particularly the chemicals that are stored for long periods of time in fat, such as dioxins and HCB, the immaturity of infant biotransformation, elimination, and other physiologic systems usually produces higher blood levels for longer periods. Additionally, developing organs and systems are more sensitive to many toxic chemicals, including dioxin and HCB. Many studies have evaluated the health effects of HCB on children after the massive poisoning in Turkey. I stated, *"Ninety five percent of children in the Turkey epidemic who developed Pembe yara (or pink sore) died."* I consider that fact alone to be sufficient evidence that children are much more susceptible to the toxic effects of HCB. Several studies show subtle toxic effects on children at very low body burdens of HCB.

Ribas-Fitó et al. (2007) found that 4-year-old children with concentrations of HCB greater than 1.5 parts per billion (ppb) at birth performed very poorly on Social Competence and had a higher risk of developing Attention Deficit Hyperactivity Disorder (ADHD). They concluded

> *These results suggest that some infants may be at risk for developing neurotoxicity from HCB due to relatively high concentrations of HCB detected in cord serum and breast milk from women in certain parts of the world.*

The findings of Ribas-Fitó *et al.* (2007) in human children is consistent with earlier studies showing rodent litters maternally exposed to HCB showed an increased risk of presenting behavioral alterations such as hyperexcitability and hyperactivity. I have concluded from this and many other studies that this is sufficient evidence that women of childbearing age (because they pass HCB to their developing fetuses), fetuses, and young children constitute a sensitive group and that even a small exposure can pose risk.

The World Health Organization (WHO) in its report, *Assessment of the Health Risk of Dioxins—Reevaluation of the Tolerable Daily Intake (TDI)* (WHO 1998) recognizes the health effects associated with background exposure levels. The WHO report states:

> *Compared to adults, the daily intake of PCDDs/PCDFs and PCBs for breast fed babies is still 1-2 orders of magnitude higher on a per body weight basis* [10 to 100 times]*...In summary, noncancer endpoints were evaluated among groups exposed to dioxins, dioxin-like and non-dioxin-like polychlorinated aromatic compounds in a variety of exposure scenarios, from background to extremely high exposures. Among children exposed in utero to background levels, effects include subtle developmental delays (U.S. and Dutch children) and subtle thyroid hormone alterations (Dutch infants to age 3 month). Multiple, persistent effects occurred among highly exposed children in Yusho and Yucheng who had transplacental exposure.*

It is noteworthy that WHO stresses these subtle toxic effects may be occurring after *in utero* and childhood exposures. They now recommend daily exposures should not exceed 1-4 picogram/kg-day, which is about the daily background exposure:

4.5.2 The FDA Is Reducing Dioxins in Food

Dr. Finley states that if background exposures were really producing toxic effects, FDA would actively be engaged to reduce exposures from food.

> *It is important to note that despite the presence of measurable levels in a variety of food products, regulatory agencies such as the U.S. Food and Drug Administration and the U.S. Department of Agriculture have not recommended that people avoid eating all such foods unless the levels exceed the established regulatory thresholds.*

In fact, FDA has been following a strategic plan to identify and eliminate foodstuffs to reduce human exposure to dioxins since 2000. The Agency's plan is titled, *DIOXINS: FDA Strategy for Monitoring, Method Development, and Reducing Human Exposure* (FDA 2002; http://www.cfsan.fda.gov/~lrd/dioxstra.html). In the section *Potential Human Health Risk,* the FDA states:

> *Scientists and health experts are concerned about dioxins because exposure may result in a variety of adverse health effects. Studies have suggested that high dioxin levels to which some*

> *industrial workers were exposed in the past led to reproductive and developmental problems, increased heart diseases, increased diabetes, and increased cancer. In 1999, the International Agency for Research on Cancer (IARC) classified one of the dioxin congeners (TCDD or 2,3,7,8-tetrachlorodibenzo-p-dioxin) as a human carcinogen [emphasis added]. In its draft dioxin reassessment, new assessments of worker populations exposed to TCDD have led EPA to suggest that TCDD may be a more potent carcinogen than had been previously thought.*

In FDA's section, *Measures of Success for Broader Monitoring Program,* the Agency states:

> *Our immediate goals are to obtain profiles of background levels in a wide variety of foods and feeds through a broader monitoring program and to identify opportunities to reduce human exposure to dioxins. Measures of success for achieving these goals will include: Identifying foods and feeds with unusually high levels of dioxins…Trace-back investigations of unusually high levels in foods and feeds to determine if the source of contamination can be reduced or eliminated…Improving assessments of human exposure to dioxins. This will enhance our ability to identify and protect susceptible populations*

In summary, FDA is engaged in a strategy aimed at identifying sources of dioxin in food and, when feasible, eliminating them. Because dioxins are so widespread in our foodstuffs, FDA cannot eliminate all dioxin from our diet. However, with the monitoring plan they have in place for the specific purpose of eliminating high dioxin sources, they are following a prudent, reasonable, and cost-effective path.

4.6 Facility Workers Have Elevated HCB Body Burdens

Dr. Finley seems unconvinced that HCB is not present in U.S. citizens despite the fact that HCB has not been detected in the general U.S. population in a sample population of almost 4,000 people.

4.6.1 NHANES Background Data

Dr. Finley makes the following critiques about my analysis:

- I didn't use the NHANES Third Edition;
- The limits of detection (LOD) in the NHANES study was too high;

- He was unable to calculate statistics for the NHANES data because the number of people with detectable HCB was "too low."

Obviously, scientists use the most recent data but I used the NHANES to stress HCB has not been detected in the U.S. general public for many years now. In fact, it has not been detected since the 1999-2000 NHANES sampling event. The more recent NHANES 2001-2002 data (Third Ed.) just confirms that finding. I am unclear about Dr. Finley's statement: ."because the proportion of results below the limit of detection was too high to provide a valid descriptive statistical result." Since HCB was not detected in nearly 4,000 U.S. citizens, no statistic could be calculated.

As for the "high LOD", it should be noted that the same CDC conducted the HCB NHANES studies and HCB analysis for Facility workers. Moreover, Dr. Finley's statement:

> *Therefore, it is inappropriate to claim that HCB body burdens in the U.S. population are zero; instead they are below the limit of detection (which was as high as 118 ng/g on a lipid basis in DeGrandchamp's referent population).*

First my point was simply that zero people in either NHANES study had detectable levels of HCB in their bodies. Second, it is not clear if Dr. Finley has closely reviewed the HCB Facility cohort data because he states the LOD was "as high as 118 ng/g (ppb)." This suggests that the "high" LOD was the problem in the NHANES study. However, this "high" LOD does not pertain to the entire population of close to 4,000 people. Additionally, the lowest detected HCB level in the Facility cohort of 253 ng/g (ppb) far exceeds 118 ppb, so if the NHANES cohort had had blood levels even close to the levels detected in the Facility cohort we would know about it.

I also provided the reason HCB is no longer detectable in the general population: The industrial production and use of HCB ceased in the mid-1970s, and EPA cancelled its pesticide registration in 1984.

4.6.2 Comparing HCB in Facility to Background

Dr. Finley states that my conversion of the HCB levels was flawed. At the time I prepared my report, I did not have access to serum blood level data. Since that time, I have acquired the data and can now make direct comparisons between the average HCB levels measured in 2002 and 2004 based on serum levels. Exhibit 15 presents the results, which confirm my earlier conclusion that the average or mean HCB serum concentrations are increasing and not decreasing.

Dr. Finley states:

> *Based on the fact that the two studies do not represent 1) the same population or 2) the entire USM population, it is scientifically invalid to conclude that body burdens in USM workers have significantly increased between 2002 and 2004.*

As I stated in my expert report, I could not make evaluations about specific workers because the Facility would not provide me with individual employee sampling results. However, since the Facility has access to sampling results they can determine whether body burdens in specific individuals participating in both studies have increased or decreased. At this time, based on limited data and information, I can only conclude that there is sufficient overlap of employees as is shown in Exhibit 15 to determine the mean concentration of the 2004 data is more than double the body burden in the 2002 samples. Moreover, the maximum body burden has increased, as well, although it cannot be confirmed that this is the same worker.

EXHIBIT 15: HCB BODY BURDENS INCREASE FROM 2002 TO 2004

	HCB SERUM LEVELS	
	2002	**2004**
	Mean Concentration	**Mean Concentration**
Maintenance	3.4 ppb	8.8 ppb
	Maximum = 20 ppb	**Maximum = 34 ppb**

In evaluating HCB body burden, my goals were very explicit (page 35):

> *For my next analysis, I compared blood levels from the two studies to determine whether HCB blood levels had declined over the two-year period from 2002 to 2004. I was interested (from an*

> *occupational health standpoint) in whether steps taken by Facility management were effective in reducing HCB exposures and body burden.*

In other words, I was interested in whether the engineering changes the Facility implemented in 2001-2002 were resulting in a *significant* drop in blood levels based on the averages in the entire cohort or similar groups within the cohort.

4.7 HCB Levels Pose Noncancer Health Hazard

Dr. Finley critiques my report for not applying "regulatory criteria" in my analysis of HCB-induced non cancer health effects. He states:

> *In contrast, Dr. DeGrandchamp concludes that high levels of risk are associated with these HCB levels based on his calculations of risk for both cancer and non-cancer effects. He does not, however, attempt to compare the directly measured values with regulatory criteria for HCB. For example, comparison of Facility HCB levels to the BAT (Biologischer Arbeitsstoff-Toleranz-Wert) value established by the DFG (Deutsche Forschungsgemeinschaft 1995, 2005) indicates that all Facility workers are within safe levels.*

I did not compare blood levels to regulatory criteria for the simple reason that none exists. I know of no U.S. health agency that either uses or acknowledges the *Biologischer Arbeitsstoff-Toleranz-Wert* value as a regulatory value. Addtionally, as a toxicologist I am not qualified to make a "regulatory" decision. Finally, the *Biologischer Arbeitsstoff-Toleranz-Wert* value for HCB is based on one study published more than 25 years ago and, according to MWH (2003) is not based on the most sensitive endpoint, which is immunotoxicity.

I identified the study of Daniel *et al.* 2001 as the principal study that should be used to derive a safe blood level for HCB. The toxic endpoint was immunotoxicity and the safe blood level is 1.1 ppb.

With regard to my HCB toxicity analysis Dr. Finley concurs:

> *In summary, I do not dispute the findings of a correlation between HCB blood levels and IFN-γ in the Daniel et al (2001) study. However, I do question the use of the average blood value observed in the Daniel et al (2001) study population as a point of departure in Dr.*

> *DeGrandchamp's non-cancer risk assessment, particularly considering its assignment as a level associated with no observable adverse health effects when the authors themselves did not characterize the endpoint examined as an adverse health effect.*

Obviously, based on the function of the immune system (which is to protect the body), any immunotoxic effect predisposes the individual to disease, cancer, infections, etc. Daniel *et al.* state:

> *This finding indicates that HCB has significant impact on Th1 lymphocytes in vivo. IFN-γ, which is produced by Th1 lymphocytes, is involved in the induction of cellular immune responses against antigens such as viruses by activating NK cells, monocytes/macrophages, and granulocytes, and humoral immune responses by increasing the immunoglobulin secretion of plasma cells.* ***Impaired IFN-γ production might favor infections*** *[emphasis added].*

Dr. Finley states that MWH (2003) estimated risks based on a "traditional" risk assessment. I agree that they conducted a thorough exposure analysis, but a toxicological analysis based on direct blood sampling data is far superior to mathematical modeling used to estimate exposures based on environmental data.

4.8 Take-Home Contamination Is a Health Threat

Dr. Finley states that my analysis of take-home contamination was seriously flawed. He had numerous critiques regarding my use of the coverall data. He suggests that Facility workers do not take contamination home with them. The coverall data and photographs I presented clearly show very high levels of both dioxin and HCB on the 3 worker coveralls. Despite this strong evidence of contaminated workers, Dr. Finley suggests the data are "useless" and should not be used for any purpose. The following are a summary of his critiques, which are baseless or misleading:

- No formal sampling plan was developed;
- I did not review and present the "correct" scientific studies;
- I used the wrong dataset, which was based on extracted soil and dirt; and
- The very high dioxins are present as part of the fabric and have nothing to do with the Facility-generated dioxins.

It is noteworthy, that the Facility's independent analyses of coverall samples also showed high contaminant levels. It is of interest that Dr. Finley does not comment on those sampling results. He does not state whether the Facility's own data, which confirm the high contaminant levels, are also useless.

Dr. Finley has misinterpreted the goals of my analyses. First, the coverall samples were collected for a very simple reason: To determine whether it was possible take home contamination could expose people outside the plant to Facility contaminants. It was not necessary to collect coverall data to evaluate worker exposures since they were evaluated directly with blood samples. Additionally, it was never my intention to use the coverall sampling data to conduct a detailed *quantitative* analysis of exposures to take home contamination and included no such analysis in my report. I simply wanted to determine whether it was possible workers had in the past, or are now taking contamination home with them which could expose their family members who may be much more sensitive.

4.8.1 Take-home contamination Studies Clearly Show Health Threat

Dr. Finley disputes my review of applicable take-home contamination studies as not applying to the Facility. He states:

> *In order to determine the likelihood of take-home contamination and family exposure to compounds at USM, Dr. DeGrandchamp first conducted a review of "all pertinent studies and peer review publications to identify studies that had similar exposure conditions," (DeGrandchamp, p. 46). In fact, Dr. DeGrandchamp devotes significant efforts to researching this topic – but not to researching dioxin and HCB take-home issues specifically.*

The studies I presented show how common and widespread take home contamination is in many different industrial sectors. What I showed is that it occurs in many different industries and there is no reason to believe the Facility is unique and immune from the problem. Despite the weight of evidence I presented, he theorizes that take-home contamination for some unknown reason does not apply to the Facility. This theory defies common sense. As I documented in my expert report, I observed and photographed Facility employees not only working in highly contaminated environments, but coming into direct contact with contamination, which resulted in highly soiled and contaminated clothing. Even a cursory glance at the Photographs in Appendix C of my expert report clearly shows their soiled and contaminated clothing and bodies as well as the general environments they are working in.

Although Dr. Finley suggests that the numerous studies on take-home contamination do not apply to the Facility workers, he does not specifically state what makes the Facility workers so unique. That is, in light of the overwhelming number of studies that involve similar working conditions and contaminants, it would be highly unusual if not impossible if Facility workers bodies and clothing *were not* contaminated at the end of their shifts.

I agree with Dr. Finley that no dioxin-specific take-home contamination studies have been published. But to conclude that because dioxin studies at other facilities have not been conducted, a take-home contamination problem does not exist at the Facility is untenable. Contaminants very similar to dioxin have been studied and they reveal the hidden health threats posed by take-home contamination. In order to directly respond to Dr. Finley's critique it is important to understand the reason *why* there are no dioxin studies. That is, dioxin exposure in the workplace is insidious and workers don't know they are being exposed. Dioxin is not used or manufactured and it is only produced as a toxic byproduct and dioxin sampling and analysis is only rarely conducted. Even when dioxin is measured in the workplace the levels cannot be easily interpreted or compared to occupational standards since none exist. Lacking motivation or regulatory incentive to monitor for dioxins in the workplace dioxin exposures go undetected. Furthermore, workers are not aware of their exposures because dioxin has no telltale odor or taste. In contrast to most studies focusing on pesticides and heavy metals, workers know from the outset they are exposed to the contaminants and workplace conditions are usually well monitored. A case in point is the lack of dioxin monitoring at the Facility. Lacking even the most basic dioxin monitoring in the workplace it is not surprising no studies have been conducted. Furthermore, since industries (such as the Facility) are unlikely to fund and support analyses of take-home contamination of dioxin, no studies will soon be available.

4.8.2 Coverall Analyses Were Optimal

Dr. Finley states that no sampling plan was developed and that samples were simply collected and analyzed in haphazard manner that deviated from standard protocols. Dr. Finley is incorrect because there are no standard protocols to deviate from. Furthermore, considerable effort was made not only to plan for the sampling event but also to refine each step of the process carefully.

First a formal sampling plan *was* developed and implemented. Furthermore, after the samples were collected, they were analyzed using routine procedures. I reviewed the peer-publications Dr. Finley cited in his report and conclude the laboratory analyses of coverall samples were performed in much the same

manner. In fact, the EPA sampling and analysis methodology was in many respects superior to the studied cited by Dr. Finley. For example, the amount of Facility coverall material analyzed was 50-100 times more than the amount of material analyzed by Horstmann and McLachlan (1995).

Contrary to the chaos implied by Dr. Finley regarding e-mails and subsequent correspondence with the laboratory, it is normal standard practice with these types of unique analyses (for which no standard procedures exist) to take all necessary steps to refine certain technical and analytical aspects of sample preparation. This is in contrast to environmental sampling of soil, air, water, etc. for which "off-the-shelf" boilerplate sampling and analysis procedures are used. It should be noted that the Facility has had the opportunity and means to independently take coverall samples for more than 3 decades to evaluate take-home contamination worker but did not do so. Now that EPA has taken the effort, the Dr. Finley considers the EPA data worthless. It is interesting that now even though Dr. Finley himself has his own coverall data from the independent analysis conducted by the Facility, he did not develop an opinion about the potential health-effects of take-home contamination apart from a critique of my opinion.

Regarding the implementation of the sampling plan, the Facility had numerous experts and Facility personnel participating in every aspect during the entire coverall sampling exercise. They observed each and every sampling step, which were further documented, and photographed. Finally, coverall samples were split, and the Facility conducted its independent analysis of the coveralls. Lastly it should be noted that after reviewing all the numerous steps involved in the complex sampling event, the most notable "problem" Dr. Finley found was that EPA did not develop a sampling plan.

Dr. Finley concludes the coverall data cannot be used even in the limited analysis I conducted. He concludes that *major* violations of sample and analysis protocols have occurred, rendering the data completely useless. I disagree with his assessment. The coverall data are unique and provide important information about take-home contamination at the Facility that we would not have otherwise. During the 3 decades the Facility has been in operation it has never investigated the health effects associated with take-home contamination. Nor has the Facility treated this health related issue as important. The only activity initiated by the Facility has been the fairly recent policy instructing workers not to take work clothes home with them to be laundered. Although I also noted workers were not showering and were likely transporting contamination home on their bodies, the Facility has yet to make showering at end of the shift mandatory (even if they made it mandatory, however, the Facility could not enforce it since it does not have sufficient showering facilities to accommodate all the workers.)

4.8.3 I Used the Correct Analytical Data

Dr. Finley critiques my use of dioxin and HCB data based on the estimated amount of dirt and dust on each sample. He suggests this data is flawed and irrelevant.

My stated goal was to determine if take-home contamination could be a health problem. Using simple common sense, it seems reasonable that coveralls taken home to be laundered would spread contamination through the house by virtue of dislodging loose contaminated dirt and dust. In lieu of going to the homes of Facility workers to collect samples (which would have been too disruptive), coverall samples were collected. For this reason, the coverall data that is most relevant to my analyses was the amount of dirt and dust measured by the coveralls. Dr. Finley considers this data to be inappropriate stating:

> *First, if my understanding of the extraction process is correct, the amount of dirt and dust on each sample as reported in Exhibit 11 is not actually an accurate representation of how much dirt and dust was on the specific coverall sample itself, nor is it an accurate representation of the dirt and dust on the full coverall worn by the worker. And, second, reporting dioxin levels associated with the "extractable" portion is wholly inappropriate given that workers are exposed to the coverall itself, not an extractable portion of the coverall, and that the extractable portion does not even represent all of the dirt and dust on the coverall.*

First, it is clear Dr. Finley has misunderstood the reason samples were collected. It is irrelevant that "workers" are exposed to the coverall itself since I am only concerned about the amount transported home to which their families will be exposed. That is, the coverall sampling has nothing to do with the worker exposure. Additionally, the extracted data are the most representative data because it represents a "real world situation." That is, when coveralls are taken home not all the loose dirt and dust come off which is best represented by the dirt that comes off. Dr. Finley states:

> *As shown in Table 6, the TEQ resulting from analysis of dioxins based on total and extractable are very different. As reported by DeGrandchamp, the total TEQ in the coveralls were 51, 11 and 19 ng/g (ppb), for the Burnett, Jones and Smith coverall samples, respectively when based on extractable weight. However, more appropriate analysis based on the total weight of the sample reveals that the total TEQ in the coverall samples was only 1.058, 0.483, and 0.105 ng/g, respectively (Table 6).*

In other words, Dr. Finley believes dioxin and HCB data should be based on the amount of *fabric* sampled. He provides no rationale for his statement. It is unclear why the total weight of the sample is more "appropriate" to address my stated objectives of determining the amount of loose dirt and dust that could be shaken off in workers homes. The total weight of the fabric is completely irrelevant to my analysis of take-home contamination because it has no meaningful relationship to the physical world. For example, Dr. Finley goes to great lengths to show fabric dyes used in manufacturing normal clothing are contaminated with dioxin. However, these dyes are physically firmly bound to microscopic fibers in the fabric and play no role in the analysis of take-home contamination. In summary, I used the correct coverall data to specifically address the issue of take-home contamination based on the best and most appropriate real world conditions.

4.8.4 Background Dioxin Levels in Fabric are Irrelevant and Insignificant

Dr. Finely attempts to obscure the finding of high levels of dioxin and HCB in Facility coverall samples by suggesting the background sources of dioxins in fabric dyes are responsible for the high levels that were detected and that the Facility is not responsible. His theory is untenable for several reasons. First, it is my understanding that employees wear Facility-provided coveralls so the Facility is responsible for any dioxins measured in the Facility coveralls. Second, I was unable to find even one study among the several he cited where any HCB was detected on any fabric sample. As I mentioned in the section on HCB body burdens, HCB and dioxins are produced together in the Facility and workers are exposed to both at the same time. Since the Facility coveralls were highly contaminated with HCB, it would be impossible for the Facility-related dioxins to not equally contaminate the coveralls. The conclusion that the Facility coveralls could be highly contaminated with Facility releases of HCB, but the dioxins are from a background source defies common sense. Third, the "background" levels associated with the fabric itself as presented in the studies discussed by Dr. Finley are for the most part negligible compared to the concentrations measured in the Facility samples. For example, most fabric concentrations of dioxin were in the very low parts per trillion. Fourth, based on the publications Dr. Finley cites the background dioxin associated with the fabric is mostly removed during the first washing of the fabric. None of the Facility coveralls were new and appeared to have been well worn and washed numerous times.

Perhaps if Dr. Finley re-evaluated the data in light of my stated objectives instead of the misunderstanding he seems to have, he would have a different conclusion. His misunderstanding is obvious in his following statement:

> *This conclusion is difficult to understand for a number of reasons. First, it is unclear why he has chosen to utilize the results of the flawed coverall sampling effort to characterize worker exposure when more accurate exposure measures were available. Generally, measurements of contaminants on coveralls are an accurate indicator of direct contact with chemicals in the workplace. Other industrial hygiene sampling efforts, such as personal air sampling and/or wipe sampling, would provide a much more accurate characterization of exposure than relying on contaminant levels on and in worker coveralls.*

As I stated numerous times in my expert report, the coverall samples had nothing to do with my evaluation of the workers. My analysis of the Facility workers was solely based on their blood samples. The coverall samples were only intended to reveal the contamination that could be taken home to contaminate their automobiles and homes.

5 SPECIFIC REBUTTAL RESPONSES TO DR. LYONS' REPORT

Dr. Lyons states the following:

> *The number of workers who are exposed to trace amounts of dioxin and other chemicals because of their jobs at USM is small. The NIOSH study identified 53 of the 400 USM workers as being at potentially high risk of exposure to trace amounts of various chemicals including dioxin.*

Dr. Lyons is mistaken; exposure to contamination is widespread as I show in Exhibit 16 (which was Exhibit 8 in my expert report). In the Facility cohort of 93 employees, 77 had detectable levels of HCB as reported in the MWH (2003) report. Furthermore, the body burden of HCB can be considered to be a good surrogate for dioxin because they are formed together during the same processes at the Facility and they have very similar fate and transport properties. That is, where workers are exposed to HCB, they are also exposed to dioxin.

EXHIBIT 16: NUMBER OF WORKERS EXPOSED TO HCB

WORKER JOB CLASSIFICATION IN BLOOD VOLUNTEER GROUP	HCB BLOOD SAMPLE RESULTS				
	NUMBER OF SAMPLES [1]	NUMBER OF SAMPLES DETECTABLE HCB	PERCENTAGE SAMPLES DETECTABLE HCB	MEAN	MAXIMUM
Maintenance	47	43	91%	4.8	20
Reactor Process	8	8	100%	5.4	16
Electrolytics	16	15	94%	4.0	14
Chemical Operations and Other Production Positions	7	2	29%	0.8	1.6
Administrative	15	4	27%	1.8	16
TOTAL	93	72	77%	3.4	20

I also stated the importance of this finding in my expert report:

> *Perhaps the most important finding, however, was the widespread dispersal of HCB contamination throughout the Plant area and into non-production areas. An unexpected finding was that employees in non-production positions (such as clerical employees) had higher mean HCH levels than Chemical Operations/Other Production Positions. Non-production employees had a mean concentration of 10 times the concentration detected in workers in Chemical Operations, and the maximum HCB blood level in employees working in Non-production areas, which included clerical workers, was 16 ppb serum.*

Dr Lyons states:

> *The mean (or average) value of dioxin found in the blood of the 30 workers was 38.2 parts per trillion (ppt) with a range of 14.0 to 130.1 ppt. (In other words one worker had a blood dioxin*

> *level of 14.0 ppt and another of 130.1 ppt, and the remaining 28 workers had blood dioxin levels somewhere between these two values.)*

Dr. Lyons incorrectly states the mean and the range of dioxins. The mean concentration is 41.5 ppt and the range is 12.9 to 175.9 ppt.

Dr. Lyons states:

> *Blood dioxin levels increase with age. Because the age categories presented by Ferriby et al. do not closely match those of the workers at the MagCorp facility, data on 170 men between ages 40-59 was extracted from the NHANES sample of 1081 to more closely match the ages of the 30 workers at the USM Rowley facility.4 The dioxin values for the U.S. population of similar age ranged from 6.8 parts per trillion (ppt hereafter) to 157.0 ppt and the mean value was 19.4 ppt. This establishes the range of blood dioxin that would be expected in a group of men of similar age in the U.S. who did not have significant occupational exposures to dioxin.*

There are several inaccuracies in this statement. First, as I previously mentioned, the Ferriby *et al.* study is appropriate because it *does closely* match the NHANES study. For example, Dr. Lyons calculates the mean for the 40-59 age group based on NHANES to be 19.4 ppt compared to 19.0 ppt reported in Ferriby *et al.* (2006). There is no difference between those values. Furthermore, Dr. Lyons reports a maximum concentration of 157.0 ppt from NHANES for men aged 40-59, while Ferriby *et al.* report a maximum of 94.9 ppt for 45-49 ppt. As Dr. Lyons states that dioxin levels increase with age, it does not seem possible that the 40-59 age group has a higher maximum dioxin concentration than the older 45-59 age group. Furthermore, Dr. Lyons does not state precisely what dioxin congeners he included in his analysis. It is also not clear whether Dr. Lyons weighted his analysis to closely represent the Facility workers because there were only 3 out of 30 workers who were aged 40-59. It should be noted that Dr. Lyons' results are considerably different from Dr. Finley's, who is the other defense expert.

It should be noted that Dr. Lyons repeatedly incorrectly states the descriptive statistics for the Facility workers on page 3. It is not clear where he derived those values. Simply put, the mean background dioxin body burden for Facility workers is 41.5 ppt compared to 19 ppt for the mean U.S. general population. In other words, the mean Facility body burden is more than twice the background levels. Due to the numerous errors he states for both the background dioxin body burden in the U.S. population as well at the Facility cohort, his conclusions regarding body burdens are untenable.

Dr. Lyons states:

> *Based on the values measured in the USM workers it is likely that the dioxin found in their blood comes from exposures outside of their employment at USM just like the U.S. population.*

Notwithstanding the statistical errors made by Dr. Lyons as stated above, which show this statement (about background levels) to be incorrect, it appears as though he has simply ignored the HCB body burden. As I discussed previously, the HCB body burdens in Facility workers are a direct result of exposure to HCB at the Facility, since HCB is not detected in the U.S. general population. As discussed, HCB and dioxin are generated from the same processes at the plant and are similarly dispersed after they are formed. They are co-localized throughout the Facility and workers come in contact with them simultaneously. Since both uncontrolled releases have similar physical properties and enter the body in a similar manner, it would be impossible for workers to contact and absorb HCB into their bodies but somehow *not* contact and absorb dioxin. The fact that HCB and dioxin body burdens are highly correlated in Facility workers means they are simultaneously contacting and absorbing HCB and dioxin. In other words, it would be impossible for workers to get HCB into their bodies without getting dioxin as well.

Dr. Lyons incorrectly labels the worker with the maximum dioxin level as an "outlier."

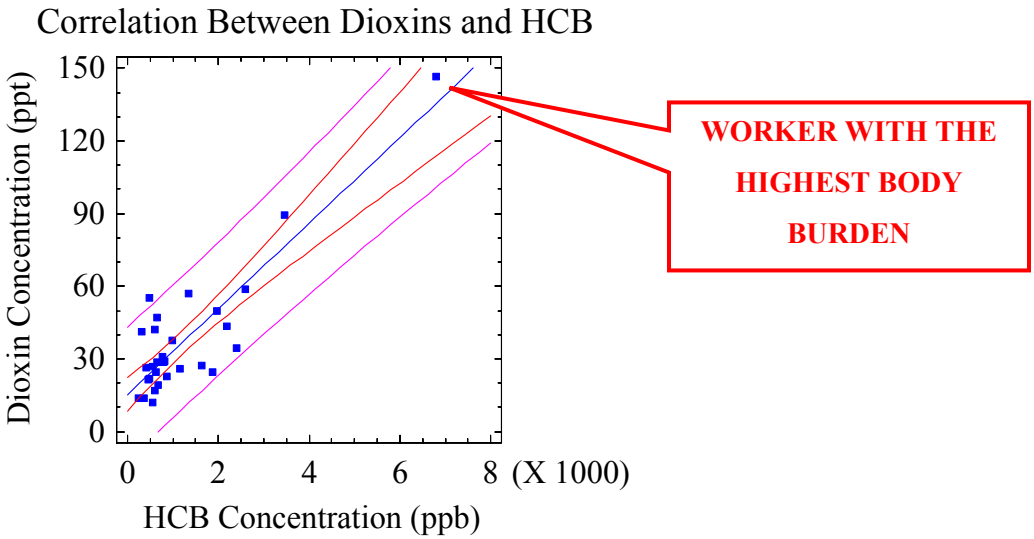
> *It is unlikely that only one of 30 high risk workers (as determined by NIOSH) is being exposed to high levels of dioxin in the workplace. This worker's dioxin level is near 5 times the median value of the other 29 workers and 1.64 times higher than the next the highest worker. Statisticians and epidemiologists who conduct studies on human populations see problems such as this worker's dioxin level so often that they have a name for it. These values are termed "outliers" because they lie so far from the upper values found in all other study subjects. The usual practice is to eliminate the "outlier"*

There are several inaccuracies in this statement. Dr. Lyons provides no evidence that this individual is truly an outlier. That is, he has conducted no statistical tests to show this individual measurement is an outlier. Scientists cannot just label a measurement an outlier because it is not the result they want it to be.

First, an outlier is defined as an artifact or an extreme value that lie far beyond the expected value. For this reason alone, the worker with the highest dioxin *cannot* be an outlier. In fact, the only way he could

be an outlier is if he *did not* have a very high level of dioxin. This is because this particular individual not only has the highest dioxin level (175.9 ppt) but also has the highest HCB body burden (6790 ppb) among the 30-worker cohort. That is, since he had the highest level of HCB, which can only come from the Facility, then he *must* have a correspondingly high concentration of dioxin. Indeed, the maximum exposed worker has precisely the dioxin concentration that we would expect based on the strong correlation between dioxin and HCB in the Facility cohort. Exhibit 17 shows this strong relationship between HCB and dioxin for the entire group of 30 workers. For each of the 30 workers, I plotted the HCB and dioxin body burden and each is represented by a blue point on the graph. The blue line represents a constant ratio between dioxin and HCB and the closer each point falls to the blue line, the higher the correlation between HCB and dioxin for that worker. As shown with the red box pointer, the maximum exposed worker with the highest dioxin body burden also has the corresponding highest level of HCB. Equally important is that his point lies very close to the blue line.

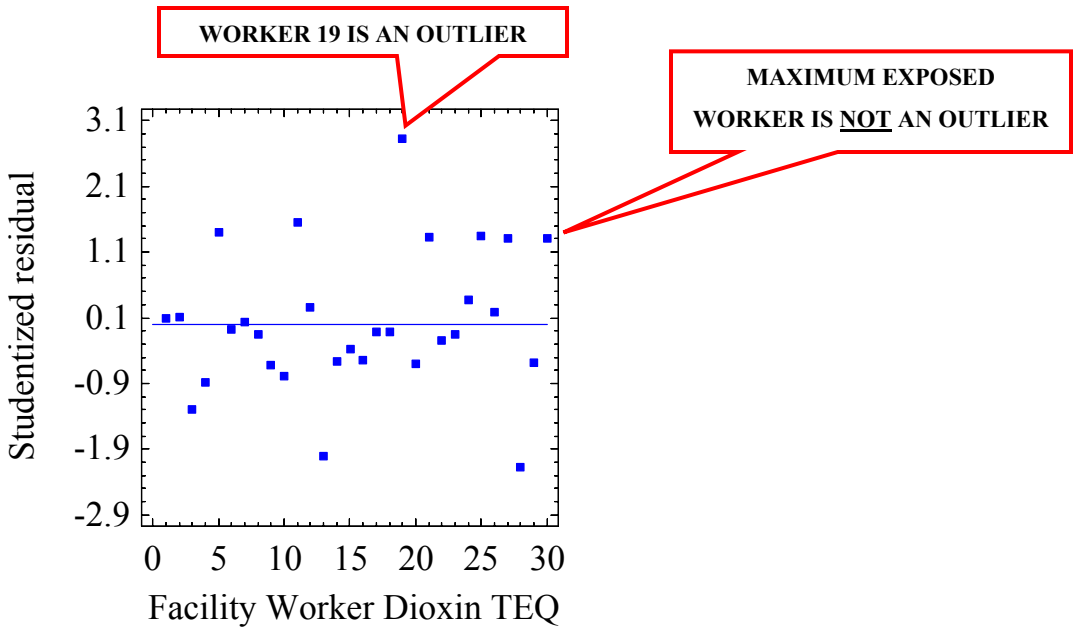
EXHIBIT 17: CORRELATION BETWEEN HCB AND DIOXIN



To directly address Dr. Lyons' conclusion that the maximum worker is an outlier or artifact, I performed a routine statistical test developed specifically to identify outliers. This test should always be carried out

to determine whether a so-called outlier is truly an outlier. With this test the difference between the *actual* body burden measured by NIOSH and the *predicted* dioxin is determined. The predicted dioxin body burden is based on the fixed ratio of dioxin-HCB that has been determined for the Facility cohort. An analogy to this type of comparison is the correlation between height and weight in a normal population. That is, knowing the height of any individual we can determine if that person is overweight. We can simply weigh them and compare their actual weight to the predicted weight based on a standard height-weight relationship. If their measured weight is greater than the predicted weight we say they are overweight, or in this case they lie "outside" the normal or expected weight. In a similar manner, I determined whether the maximum exposed Facility worker is an outlier by performing an outlier test. Exhibit 18 shows the results from the outlier test. The point representing each worker is clustered around the blue line. The closer each point is to the blue line, the closer the actual measured dioxin level is to the predicted level. The points that lie far from the blue line indicate measured levels that are not close to the predicted value. These points are then labeled "outliers." Scientists consider points lying *outside* 2-2.5 standard deviations away from the blue line to be statistical outliers. Consequently, Exhibit 18 proves the maximum individual is *not* an outlier since that point lies well within 2 standard deviations. The only outlier in the Facility cohort was worker number 19 who had an elevated dioxin body burden of 63 ppt and a Studentized residual of 2.8 ppt. Therefore, Dr. Lyons has incorrectly labeled the maximum exposed individual an outlier.

EXHIBIT 18: MAXIMUM WORKER IS NOT AND OUTLIER



Accordingly, Dr. Lyons' "rationale" (pg. 5) for why the maximum exposed individual is an outlier is also incorrect:

> *The high level found in the "outlier" may be a testing error or may result from exposure to other sources of dioxin including the regular use of a wood burning stove or fireplace, regular eating of game meats, or doing home pottery.*

Dr. Lyons' states:

> *Dr. DeGrandchamp, the Government's expert witness5 has claimed that dioxin at the USM facility is producing "an exceptionally high cancer risk" and high risk of other diseases in the USM work force.6 This conclusion is based on a single measurement of dioxin from this worker, and is scientifically unsound for the reasons mentioned above.*

In response to these critiques by both Dr. Lyons and Dr. Finley I have re-calculated both the average and maximum cancer risk for the Facility cohort. The average and maximum *Facility-related* cancer risk (background risks subtracted) for the average and maximum exposed workers is 1.1 per-one-thousand (1.1E-3) and 7.7 per-one-thousand (7.7E-3). Thus, even the average cancer risk poses an unacceptable cancer risk.

Dr. Lyons states:

> *Dr. DeGrandchamp is also generalizing from a single blood sample, one that is likely unreliable, and is applying it to others whose dioxin levels are well within the range found within the U.S. population. The justification offered is that the discipline of toxicology must protect 95% of those exposed.*

The workers' dioxin body burdens are *not* "well within" background levels. I offered no such justification. Regardless of discipline, all health professionals should be committed to protecting <u>*all*</u> exposed individuals in the workplace. The 95% citation Dr. Lyons refers to pertains, only to the general practice of evaluating *hypothetical* individuals for which mathematical models are used to *estimate* exposures. In this case, each worker gave a blood sample and dioxins and HCB were directly measured from that sample. As I have proven above, the measurement for Worker #30 represents his actual body burden and is not an artifact. Dr. Lyons statement suggests he considers Worker #30 to be a statistic and not an actual person.

Dr. Lyons states:

> *The statement assumes a normal distribution of values, not one distorted by "outlier" values, which is the case here.*

Not only is the maximum exposed Facility worker *not* an outlier, but also his measurement does not significantly distort the distribution of body burdens. To prove it does not "distort" the population statistics of the Facility cohort as a group, I re-calculated the mean concentration of the Facility workers after removing the datum for the maximum exposed worker from the dataset. The average dioxin body burden decreased only slightly from 42 to 37 ppt. Even after trimming the high value from the dataset, the mean Facility background of 37 ppt is still significantly higher than the mean background level of 19 ppt.

Dr. Lyons includes a lengthy section titled: *Information on Dioxin from Animal Studies* (pg.6). I am not clear on the interpretation of this section since I did not rely on animal data, nor to my knowledge did Dr. Finley. It is unclear why he discusses this topic. Also, within the section on "animal studies," he addresses the issue of linear low-dose extrapolation by stating:

> *…data from higher doses causing effects and assumes a linear reduction in risk as dose is reduced. This type of linear extrapolation is commonly used by regulatory agencies and is the default model used by the EPA, and is called the linear multistage model of risk. This model of risk is obviously quite limited.*

Again, it unclear why he is making such statements since I did not rely on either animal data or linear low-dose extrapolation.

Dr. Lyons states:

> *Given the low level of exposure found by the NIOSH study among the workers at the USM facility, not one worker fits into the category of someone with "relatively high body burdens of TCDD" (which is included in my definition of dioxin) which the NAS committee believes may have an association with an increase in cancer mortality.*

This is an inaccurate statement and I previously presented evidence to show that cancer has been detected at body burdens corresponding to the *average* body burden levels in the Facility cohort. The average body burden in the Facility cohort is significantly higher than the ED01.

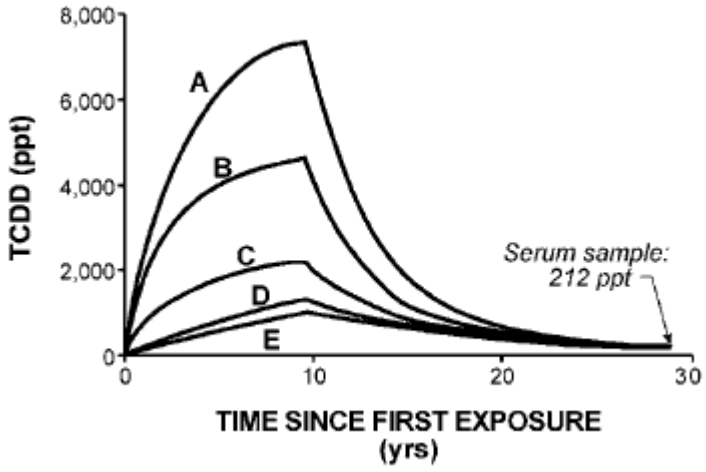
Dr. Lyons states:

> *Steenland study on 5% (170 of the 3538) its workers. The mathematical model used by Steenland et al., has been criticized by others because it substantially underestimated the level of dioxin that would have existed at the time of exposure.*

This statement incorrectly characterizes the Steenland *et al.* study. Although some recent longitudinal studies (Aylward 2005, Edmond 2004,2005) have shown a clear dose dependent elimination there is no evidence that they can or should be applied to the Steenland *et al.* study. That is, several studies have shown that individuals with very high (thousands of ppt) dioxin levels eliminate dioxin at a much faster

rate than previously thought (with an average half-life of about 7 years) those were longitudinal studies where the elimination rate could be directly evaluated with serial blood samples. The Steenland *et al.* study was a dose reconstruction based on a single measurement in time and the original body burden concentration at "time zero" cannot be determined with certainty. Although it is possible the concentrations were higher, there is no evidence to show that they were. This phenomenon is illustrated in Exhibit 19, which represents a single measurement of dioxin of 212 ppt approximately 30 years after the first exposure. The curved lines labeled A-E represents the range of exposures from high (A) to low (E) exposures, which reach a peak at about 10 years when exposure stops. From 10 years to 30 years represents the elimination from the body. The important feature is that A-E exposures lead to the point at 30 years where the single measurement was taken

EXHIBIT 19: BACK-CALCULATED BODY BURDEN FOR ONE INDIVIDUAL USING THE CONCENTRATION-DEPENDENT MODEL AS OPPOSED TO CONSTANT ELIMINATION, AYLWARD *ET AL.* (2005)



Collectively, the recent studies have only suggested that it is possible for the "back-calculated" body burdens at 10 years to be higher. However, after reviewing the pertinent studies I have concluded it is

premature to consider the Steenland studies as "wrong." Cheng *et al.* (2006) have developed a mathematical model and revisited the Steenland data and present interesting findings and assuming different rates of elimination yield slightly different results. However, in responding to the Cheng *et al.* (2007) results Steenland and Bartell (2007) state:

> *The plausibility of the findings in the current article depends, then, on the plausibility of the more complicated multicompartment pharmacokinetic model (with concentration dependence). This model was presented in Aylward et al. (2005), and is based on some animal evidence and on a small number of observations from humans with repeated measures from Seveso, as reported originally by Michalek et al. (2002). The human data consisted of data on 39 people, 36 from Seveso, with repeated dioxin measurements. with repeated dioxin measurements. Only some of these had three measurements, including one at the beginning of exposure, data that are needed to show more rapid elimination at the beginning. Michalek et al. (2002) reported that the rapid elimination of dioxin shortly after exposure occurred only in the Seveso men (N = 14), and not in the women. Furthermore (see Fig. 3 in Michalek et al. 2002), the early sharp drop in dioxin level among men is seen in only seven men who have dioxin measured three times. times. One might hesitate to draw a conclusion that the multicompartment model by Aylward et al. is superior to a one-compartment model based on so few observations… In sum, we believe that the authors use a multicompartment dose-dependent model that has only limited justification from human data, which should lead to caution in interpreting the results in Cheng*

Aylward *et al.* (2007) responded by stating:

> *However, mechanistic understanding and available sampling data support a conclusion that back-calculation over decades using a simple first-order half-life of 7.5 or 8.7 years (as used by the NIOSH researchers) greatly underestimates maximum exposures in highly exposed individuals. The magnitude of underestimation, a factor of 5– 10 or more (Aylward et al., 2005b), is substantial and meaningful in the context of risk assessment. We believe that elucidation of the impact of choices and uncertainties in exposure modeling is an important component of translating the results from occupational cohort mortality studies to the general population.*

Clearly there is some uncertainty surrounding this issue. However, as noted by Aylward *et al.* if exposures in the Steenland *et al.* study have only been underestimated by a factor of 5-10 it would have little impact on my cancer risk estimates.

Dr. Lyons states:

> *There is little information on the effects of exposure to trace levels of HCB in the occupational literature. All information has come from inadvertent exposure of nonworking populations. In Turkey, the diversion of seed grain treated with HCB as a fungicide during a famine in the late 1950's20 to bread production, caused many people to become sick and provided information concerning the effects of extremely high doses of HCB.*

Although the Turkey episode yielded important toxicological data, this statement is simply not correct. There have been numerous studies in workers and exposed populations.

Dr. Lyons states:

> *Based on these two studies, little can be determined about the health hazards of exposure to trace levels of HCB.*

This is incorrect. There have been several studies showing health hazards at very low body burdens. I discussed the Daniel *et al*. (2001) study and Dr. Finley concurred with the correlation between HCB levels and immunotoxicity stating:

> *In summary, I do not dispute the findings of a correlation between HCB blood levels and IFN-γ in the Daniel et al (2001) study. However, I do question the use of the average blood value observed in the Daniel et al (2001) study population as a point of departure in Dr. DeGrandchamp's non-cancer risk assessment, particularly considering its assignment as a level associated with no observable adverse health effects when the authors themselves did not characterize the endpoint examined as an adverse health effect.*

All 30 workers in the Facility cohort had blood levels above 1.1 ppb which was the level reported by Daniel *et al.* (2001) that produced immunotoxic effects.

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