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NATIONAL HEALTH AND ENVIRONMENTAL EFFECTS
RESEARCH LABORATORY
RESEARCH TRIANGLE PARK, NC 27711

Neurotoxicology Division, MD-74B

MEMORANDUM

Date: 13 November 2001

Subject: Benchmark dose calculations on thyroid histopathology from 1998 data reported after review by Pathology Working Group (Wolf, 2000)

From: Andrew M. Geller
Neurotoxicology Division, MD -74B
National Health Effects and Environmental Research Laboratory

To: Annie M. Jarabek
National Center for Environmental Assessment, MD - 52

As recommended at the external peer review (Research Triangle Institute, 1999), a Pathology Working Group (PWG) was convened at the National Institute of Environmental Health Science (NIEHS) to arrive at a consensus on nomenclature and a scoring system for thyroid histopathology across the studies previously analyzed (USEPA, 1998). Analyses presented herein represent new analyses using the results of the NIEHS PWG (Experimental Pathology Laboratories, 2000; Wolf, 2000, 2001).

Benchmark doses (BMDs) and the lower confidence limits on the benchmark dose (BMDL) were calculated on thyroid histopathology data from the set of six toxicity studies (reported in Wolf, 2000, 2001) submitted to the US Environmental Protection Agency (USEPA) as part of the 1998 perchlorate risk assessment effort. These calculations used incidence of thyroid pathology as rated by the NIEHS Pathology Working Group convened to review these studies (Experimental Pathology Laboratories, 2000; Wolf, 2000,2001). BMDs and BMDLs were generated for the incidence of colloid depletion, hypertophy, and hyperplasia using the summed male and female incidence data from each study, as had been done for the 1998 risk

characterization of ammonium perchlorate (AP) (Geller, 1998). While in some cases, males were more sensitive than females (data not shown), in many cases fits to separate male and female data resulted in non-convergence or produced extreme values. The benchmark estimates made with the combined male and female data generated fewer extreme values and greater convergence than those from the males and females apart. These are presented below.

BMD/BMDL were generated using the BenchMark Dose Software v. 1.30, publically available from the USEPA. A criterion of a 10% increase in incidence over controls, i.e., BMD10, BMDL10, was adopted for all studies. Data were fit with a Weibull function

$$P(\text{response}) = \text{bckgrd} + (1 - \text{bckgrd})*(1-e^{(-\text{slope}*\text{dose}\wedge\text{power})})$$

The Weibull function was chosen as a flexible form given the nature of the observed responses; i.e. non-linear monotonic functions. Except where noted, the "power" parameter of the fit was not restricted to be ≥ 1, since in many cases this restriction prevented convergence. A chi-squared test was used to determine the goodness-of-fit of these functions. Where the fit to the data did not reach a $p > 0.05$ criterion, the results of the fit are not reported.

Table 1 lists the BMD, BMDL, and goodness-of-fit probability for each study, referencing the pathology incidence tables from Wolf (2000). The Wolf (2000) re-evaluation of the thyroid histopathology data added an endpoint, colloid depletion, and separated thyroid hypertrophy and hyperplasia, which had been combined in the earlier assessment of these specimens (USEPA, 1998). These BMD and BMDL are plotted in Figure 1. Note that for the Subchronic 14- and 90 day studies and the Neurobehavioral PND 5 sample, the BMD and BMDL determinations are similar to those calculated after the initial thyroid histopathology reading (Geller, 1998, USEPA, 1998). The ranges of the BMDL values for the rat studies are also listed in Table 1. Both colloid depletion and thyroid hypertrophy yield BMDL values of approximately 0.01 mg/kg AP at the lower end of their ranges. The lower range value for hyperplasia is lower still, but this is based on a relatively poor fit. Figure 2 plots the percentile statistics of the BMD and BMDL from the combined rat studies for colloid depletion, thyroid hypertrophy and thyroid hyperplasia. Once again, this figure illustrates that colloid depletion and hypertrophy are approximately equally sensitive to the effects of AP in rats, while the incidence of thyroid hyperplasia increases over controls at slightly higher doses. The BMDL10 are quite consistent across studies, with the range of values from 25th to 75th percentile covering only 0.69, 0.30, and 1.78 mg/kg/day for colloid depletion, hypertrophy, and hyperplasia, respectively. Note that the BMDs and BMDLs calculated before the thyroid histopathology slides were reviewed by the PWG fairly well encompass the values generated after the PWG review (Figure 2).

References

Experimental Pathology Laboratory, Inc. 2000. Pathology Working Group report.

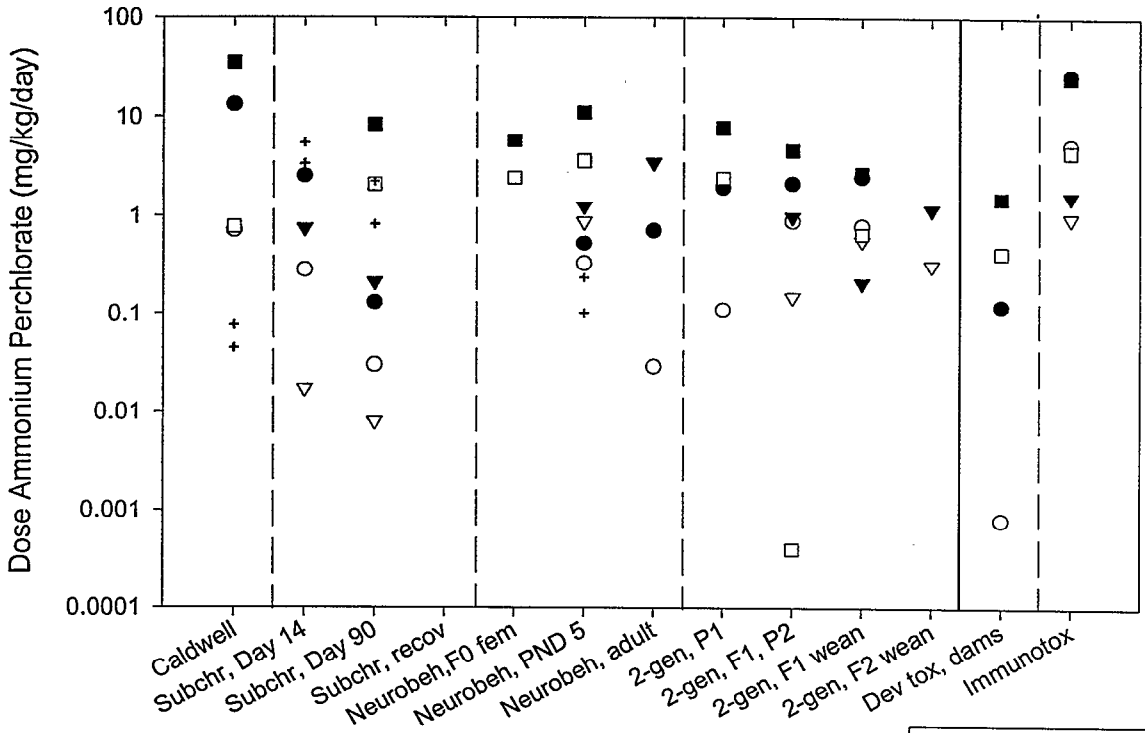
Geller, A.M. 1998. Benchmark dose calculations on thyroid data from studies submitted for evaluation of perchlorate. Memorandum, 28 December 1998.

USEPA Perchlorate Environmental Contamination Toxicological Review and Risk Characterization Based on Emerging Information. Office of Research and Development, U.S. Environmental Protection Agency, 1998.

Wolf, Douglas C. 2000. Report of the peer review of the thyroid histopathology from rodents and rabbits exposed to ammonium perchlorate in the drinking water. Memorandum, 5 May 2000.

Wolf, Douglas C. 2001. Erratum to the Report of the peer review of the thyroid histopathology from rodents and rabbits exposed to ammonium perchlorate in the drinking water. Memorandum, November, 2001.

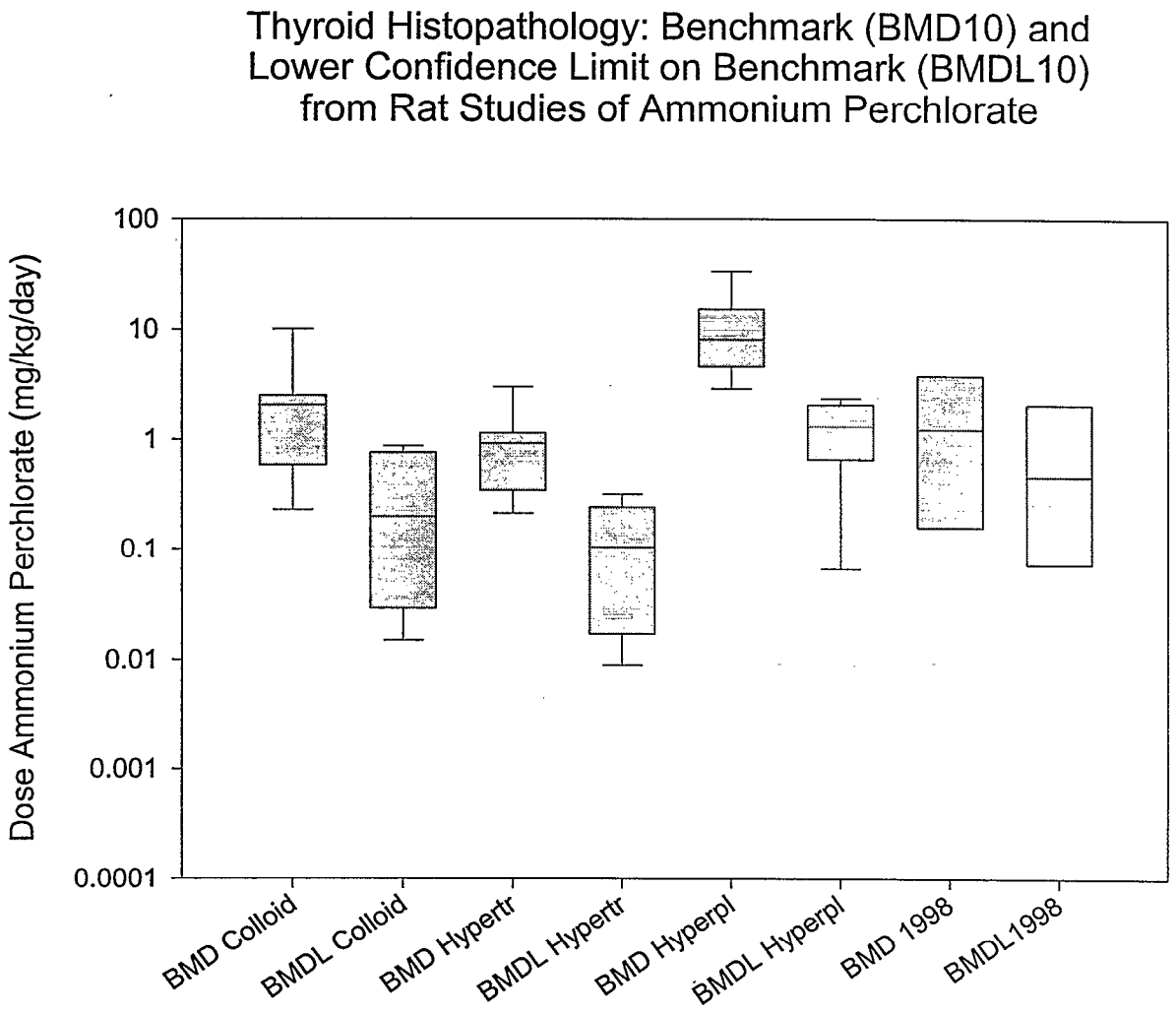
Benchmark Doses for Incidence of Thyroid Histopathology



BMD10 and BMDL10 for incidence of colloid depletion, thyroid hypertrophy, and thyroid hyperplasia in 6 studies submitted to USEPA for the perchlorate risk characterization. Values used are tabulated in Table 1. Values to left of solid line are from rat studies. Values to right are from rabbit (Dev tox) and mouse (Immuntox). + marks BMD and BMDL from 1998 risk chacterization of ammonium perchlorate (Geller, 1998) (lesser value = BMDL; greater value = BMD)

Solid symbols -- BMD10
Open symbols -- BMDL10
○ Colloid Depletion
▽ Hypertrophy
□ Hyperplasia

Figure 1



Distribution of BMD and BMDLs for Colloid (depletion), Hypertr (i.e., hypertrophy), and Hyperpl (i.e., hyperplasia) from rat studies 1, 2, 3, 6, 7, 8, 9, 10, 11 from Table 1. Study 5 is not included because of the non-monotonicity of the data.
The boundary of the box closest to zero indicates the 25th percentile, a line within the box marks the median, and the boundary of the box farthest from zero indicates the 75th percentile. Whiskers above and below the box indicate the 90th and 10th percentiles. The rightmost boxes plot values from the combined rat studies from the 1998 risk characterization of ammonium perchlorate (Geller, 1998: USEPA, 1998).

Figure 2

Table 1: Benchmark dose and benchmark dose lower confidence limits from thyroid histopathology data after dosing with ammonium perchlorate. Fit with Weibull function, with no restriction on the exponent value unless otherwise noted. Male and female combined unless otherwise indicated.

Study Name Wolf, 2000 Table No.	Dose Levels AP Tested mg/kg/day	BMD / BMDL / χ^2 p-value exponent of Weibull fit		
		colloid depletion	hypertrophy	hyperplasia
1. Caldwell Tbls. 1 and 2	0, 1.25, 5, 12.5, 25, 50, 125, 250	13.29 | 0.72 | 0.97 4.37	Eval. not reliable due to staining (Wolf, pers. comm.)	35.29 | 0.78 | 0.20 0.88
2. Subchronic, 14 day Tbls. 3 and 6	0, 0.01, 0.05, 0.2, 1.0, 10.0	2.55 | 0.28 | 0.20 0.74	0.75 | 0.017 | 0.54 0.78	No effect
3. Subchronic, 90 day Tbls. 4 and 7	0, 0.01, 0.05, 0.2, 1.0, 10.0	0.13 | 0.03 | 0.70 0.50	0.21 | 0.008 | 0.74 0.55	8.36 | 2.09 | 1.00 7.87
4. Subchronic, 120 day Tbls. 5 and 8	0, 0.05, 1.0, 10.0	No effect	No effect	No effect
5. Neurobehav., F0 Fem. Tbl. 9	0, 0.1, 1, 3, 10	No effect	No effect	No effect
6a. Neurobehav., PND 5 Tbls. 10 and 11	0, 0.1, 1, 3, 10	0.53 | 0.33 | 0.67* 1.0	1.27 | 0.88 | 0.26* 1.0	11.02 | 3.62 | 0.32* 1.0
6b. Neurobehav., PND 5 Tbls. 10 and 11	0, 0.1, 1, 3, 10	0.45 | 0.009 | 0.46 0.94	0.92 | 0.24 | 0.24 0.81	15.18 | 1.86 | 0.70 0.36
7. Neurobehav., adult Tbls. 12 and 13	0, 0.1, 1, 3, 10	0.72 | 0.029 | 0.23 0.89	3.48 | NC | 0.72 0.29	No effect
8. 2-gen., P1 Tbls. 14 and 15	0, 0.3, 3, 30	1.97 | 0.11 | 0.68 3.84	Poor fit	7.89 | 2.44 | 0.41 0.72
9. 2-gen., P2 Tbls. 16 and 17	0, 0.3, 3, 30	2.16 | 0.90 | 0.06 1.16	0.99 | 0.15 | 0.67 0.70	4.62 | 0.0004 | 0.14 0.31
10. 2-gen., F1 weanling Tbls. 18 and 19	0, 0.3, 3, 30	2.51 | 0.80 | 0.17 1.2	0.21 | 0.057 | 0.40 0.79	2.74 | 0.66 | 0.85 0.52
11. 2-gen., F2-weanling Tbls. 20 and 21	0, 0.3, 3, 30	poor fit	1.19 | 0.32 | 0.25 0.52	No effect
BMDL Range: Rat Studies		0.009 - 0.90	0.008 - 0.74	0.0004 - 3.62
12. Dev tox., rabbit dams Tbl. 22	0, 0.1, 1, 10, 30, 100	0.12 | 0.008 | 0.19 0.36	Poor fit	1.53 | 0.42 | 0.13 0.61
13. Immunotox. Mice, combined studies Tbl. 23	0, 0.1, 1, 3, 30	26.07 | 5.15 | 1.00 7.88	1.62 | 0.97 | 0.58 0.84	24.92 | 4.48 | 1.00 7.86

Poor fit: $p < 0.05$ for χ^2 test.
* Exponent in Weibull fit restricted to ≥ 1.0.
No effect: either no incidence of endpoint noted in animals tested or no notable difference between dosed and controls.