16.0 ALZHEIMER'S DISEASE

STATEMENT TO THE PUBLIC

Alzheimer's Disease)

The reviewers used two distinct sets of guidelines to evaluate the evidence:

- *Using the guidelines that the International Agency for Research on Cancer uses to assess cancer risks, they considered the evidence as "inadequate" to implicate EMFs. This was similar to conclusions by work groups of NIEHS in 1998 and of NRPB in 2002.*
- *Using the Guidelines developed especially for the California EMF Program one DHS reviewer was "close to the dividing line between believing and not believing" that exposure to EMFs at home or work could add to an individual's lifetime risk of contracting Alzheimer's disease and the other two were "prone not to believe" that EMFs conveyed any risk for this disease.*

The reviewers graphed their degree of certainty for the purposes of policy analysis as follows:

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFS) INCREASES DISEASE RISK TO SOME DEGREE
Alzheimer's				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	

16.1 THE PATTERN OF EPIDEMIOLOGICAL EVIDENCE

Figure 16.1 Relative Risks Reported In Alzheimer's EMF Studies

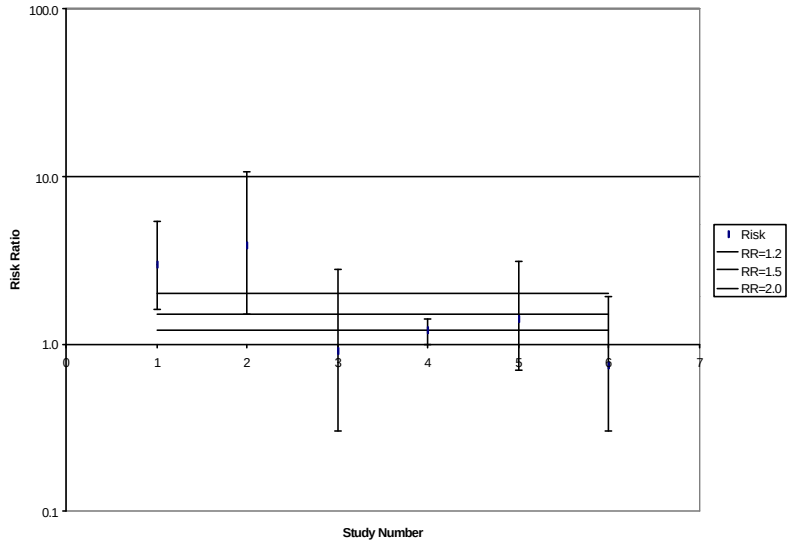

TABLE 16.1.1 KEY TO FIGURE 16.1.1

STUDY	NO	INDIVIDUAL ODDS RATIO	LOWER CL	UPPER CL
(Sobel et al., 1995)	1	3.00	1.60	5.40
(Sobel et al., 1996)	2	3.90	1.50	10.60
(Feychting et al., 1998b)	3	0.90	0.30	2.80
(Savitz et al., 1998b)	4	1.20	1.00	1.40
(Savitz et al., 1998a)	5	1.40	0.70	3.10
(Graves et al., 1999)	6	0.74	0.30	1.90

TABLE 16.1.2 DESCRIPTION OF ALZHEIMER'S STUDIES.

REFERENCE	STUDY POPULATION AND SUBJECT IDENTIFICATION	DEFINITION AND ESTIMATION OF EXPOSURE	STUDY DES.	NUMBERS	RESULT RR (95% C.L.)
(Sobel et al., 1995)	Study population: not specified. Cases: 3 series of AD patients examined, 1977-1993, at one neurological clinic in the US and 2 in Finland. Controls: 3 series: 1) vascular dementia patients; 2) patients without neurological disease; 3) neighborhood controls.	Interview data on primary occupation. Classification into high/medium vs. low EMF exposure.	CC	386 cases (36 exposed) 475 controls (16 exposed)	3.0 1.6-5.4
(Sobel et al., 1996)	Study population not specified. Cases: patients with probable or definite AD treated at AD medical center in California, US Controls: patients who were cognitively impaired or demented.	Statewide data form information on primary occupation. Classification into high/medium vs. low	CC	326 cases 152 controls	3.9 1.5-10.6
(Feychting et al., 1998b)	Study population: sub sample of the Swedish Twin Registry. Cases: identified through a screening and evaluation procedure. Controls: intact twins with 1 twin in each of 2 control groups where both were eligible.	Interviews. Primary and last occupation. Classification into 3 levels, based on JEM, highest > 0.2 μT.	CC	55 cases 228 and 238 controls	0.9 (primary) 0.3-2.8 (similar with other control group)
(Savitz et al., 1998b)	Male population in 25 states, US, 1985-1991. Cases: deaths from AD. Controls: deaths from other causes.	Job title on death certificate: electrical occupation in aggregate and individual jobs.	CC	256 cases in electrical occupation in aggregate	1.2 1.0-1.4
(Savitz et al., 1998a)	Male employees at 5 US utility companies, 1950-1988. Cases: deaths with AD mentioned on death certificate, identified through multiple tracking sources.	Measurements and employment records. Combination of duration and EMF index.	Cohort	16 cases with > 20 years in exposed occupation	1.4 0.7-3.0

REFERENCE	STUDY POPULATION AND SUBJECT IDENTIFICATION	DEFINITION AND ESTIMATION OF EXPOSURE	STUDY DES.	NUMBERS	RESULT RR (95% C.L.)
(Graves et al., 1999)	Members of a Seattle, WA, HMO. Cases of AD using NIH criteria. Healthy controls matched on age & sex.	Complete job and job title history. Each title assigned one of 3 ranks: 0 = background; 1 = intermittent; 2 = prolonged high fields	CC	89 controls 89 cases	0.74 0.29-1.92

Four out of the six studies have ORs above 1.00 (p = 0.23). Ahlbom (Ahlbom, 2001) calculates a summary OR for the two clinic-based Sobel studies of 3.2 (1.9-5.4). There seems to be true heterogeneity in these studies, related to the study design. The evidence is discussed below.

16.2 ARGUMENTS FOR AND AGAINST CAUSALITY

TABLE 16.2.1

CHANCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) Of the six studies reviewed, only two showed a statistically significant association. The others show no statistically significant effect.	(F1) Of the six studies reviewed, four showed RRs above 1.0; and, if one counts Feychting's RR of 2.7 for "last occupation," five of six reported RRs above 1.00. The cumulative binomial probability of this is 0.09, not conventionally significant, but also unlikely by chance.	(C1) One can argue about the pattern of the entire data, depending on whether one focuses on EMF as a cause of all dementias or specifically of Alzheimer's. However, at least some of these studies cannot be easily dismissed as due to chance.
(A2) The population-based studies show no statistically significant results.	(F2) It helps to see the overall pattern of association. Ahlbom (2001) also combined clinic-based studies (OR = 3.2; 95% CI: 1.9-5.4) and the pre-1999 population-based studies (OR = 1.2; 95% CI: 0.7-2.3) for a more refined look.	
(A3) One should not pool results of studies with different study designs, such as those considered here.	(F3) For all dementias, Feychting (Feychting et al., 1998b) reports an RR of 3.8 (1.4-10.2) for high EMF "last" occupations.	
(A4) One should not lump all dementia and Alzheimer's, or primary occupation and last occupation, in analyzing studies.		
(A5) The small Graves (Graves et al., 1999) study, which suggests a protective effect, emphasizes the randomness of the pattern of results.		

TABLE 16.2.2

BIAS		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The two studies with the statistically significant RRs used clinic-based controls, which are subject to selection bias.	(F1) While clinic-based case control studies have a generically greater probability of bias, as alleged in A1 and A2, there is no identifiable scenario which would predict such a bias for clinics in both California and Finland. The association with last occupation (which on average lasted a long time) found in Feychting's (Feychting et al., 1998b) population studies suggests that bias is NOT the explanation.	(C1) The strongest associations were in the bias-prone clinic-based case-control studies. The small Feychting study, with good systematic diagnosis and population control groups, suggests an association between both dementia and Alzheimer's dementia (NS) and the last occupation (median duration 25 years). Bias cannot be ruled out from the strongest studies. The small Graves study, within a defined cohort, is inconsistent with the Sobel studies. However, the Graves study defined exposure differently.
(A2) Feychting (Feychting et al., 1998b) and Graves (Graves et al., 1999) drew cases and controls from defined populations and had careful diagnostic criteria for cases. They did not show large associations with usual occupation. This suggests that there is a problem with the two studies that used clinic-based controls.	(F2) Different definitions of "electrical occupation" will have different prevalence rates. One needs to compare cases and controls using the same definition. This was done in each of these studies.	
(A3) The subtle differences in the proportion of cases and controls with occupations whose average fields exceed 2 mG are small, compared to the differences in control groups in the various studies. These are around 3%-5% for Sobel (Sobel et al., 1995), (Sobel et al., 1996), 20% for Feychting (Feychting et al., 1998b) about 7% for Savitz (1998), and about 22% for Graves (Graves et al., 1999).		

TABLE 16.2.3

CONFOUNDING		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) One does not know all the causes of Alzheimer's and cannot control for them.	(F1) Known correlates were adjusted for in these studies.	(C1) There is little or no evidence to suggest confounding as a problem here.
(A2) Shocks and contact currents, not magnetic fields, might be the explanation.	(F2) The evidentiary base linking shocks and contact currents to Alzheimer's and magnetic fields is absent.	(C2) Alzheimer's is not well enough understood for one to be sure everything has been controlled for.

TABLE 16.2.4

STRENGTH OF ASSOCIATION		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The associations are not so large that unspecified bias or confounding could be ruled out as an explanation	(F1) The Sobel (Sobel et al., 1995), (Sobel et al., 1996) associations are quite large.	(C1) Clinic-based studies such as those of Sobel, while well above the resolution power of the population studies, are more subject to selection bias. The population studies have ORs closer to 1.0 and are more vulnerable to unspecified bias.

TABLE 16.2.5

CONSISTENCY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is inconsistency in the population-based and clinic-based studies.	(F1) The clinic-based studies show strong associations. This should boost our confidence.	(C1) The Feychting (Feychting et al., 1998b) and Graves (Graves et al., 1999) studies are drawn from an identified population and have good diagnostic criteria but are small. They show associations with Alzheimer's that are below the null while Sobel's studies (Sobel et al., 1995), (Sobel et al., 1996), with clear diagnostic criteria, have associations well above the null. The rest of the studies have less-exact diagnoses and weaker associations. There is something here, but it is inconsistent.
(A2) The population-based studies have a weak to null association and make one worry about bias.		(C2) Examining the pattern of ORs, the binomial conditional probability of the observed ORs, given the hypothesis that the true OR is 1.0, is 0.34. The results are not consistent.

TABLE 16.2.6

HOMOGENEITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) The Sobel (Sobel et al., 1995), (Sobel et al., 1996) studies are the only positive studies. The other four are non-supportive.	(F1) With the exception of Graves (Graves et al., 1999), which used a different exposure approach, the studies are not completely null.	(C1) There is a lack of homogeneity in results from the studies in non-null results, a lack that seems correlated with study design. Sobel's two clinic-based studies provide larger effects than the other studies.

TABLE 16.2.7

DOSE RESPONSE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is not a clear monotonic dose response in any of the studies.	(F1) The study designs did not provide a good chance to demonstrate a clear dose response.	(C1) The studies would not be expected to show a clear dose response because the exposure assessment was not refined. This criterion is not very helpful in this context.

TABLE 16.2.8

COHERENCE/VISIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) If EMFs causes Alzheimer's, why has there been no epidemic of Alzheimer's?	(F1) There is an epidemic.	(C1) There is no consensus that the age-specific incidence of Alzheimer's is increasing. Although, as the population ages, the number of CASES is increasing.
		(C2) The occupations in the Sobel (Sobel et al., 1995), (Sobel et al., 1996) studies are infrequent enough that they would not affect the overall Alzheimer's rates much. The smaller associations in the other studies also would not affect the overall prevalence much.

TABLE 16.2.9

EXPERIMENTAL EVIDENCE		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
No evidentiary base.	No evidentiary base.	(C1) No animal pathology studies with EMF.

TABLE 16.2.10

PLAUSIBILITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) There is no reason to believe that EMFs influence Alzheimer's.	(F1) Some experiments suggest EMF effects on calcium transport, and calcium transport plays a role in Alzheimer's.	(C1) The evidence linking EMFs to calcium and immune function is still contested, so mechanistic explanations are still speculative.
	(F2) Some experiments suggest that EMFs affect immune response, and immune response may be important in Alzheimer's.	

TABLE 16.2.11

ANALOGY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
None.	None.	See Generic Issues chapter.

TABLE 16.2.12

SPECIFICITY		
AGAINST CAUSALITY	**FOR CAUSALITY**	**COMMENT AND SUMMARY**
(A1) One of Sobel's comparison groups (Sobel et al., 1995) consisted of patients with other dementias, and the relative risk between these to groups of patients was similar to that between Alzheimer's patients and healthy controls. That would suggest that EMFs don't do not cause non-Alzheimer's dementia. However, Feychting (Feychting et al., 1998b) shows the strongest association between electrical occupation and non-Alzheimer's dementia. Thus, there is inconsistency as to which disease is associated.	(F1) There were only 70 subjects in the Sobel control group. When compared to the 299 non-dementia controls, there IS a weak association, 1.3 (0.3-5.3) for primary occupation exposure above 2 mG.	(C1) The lack of consistency between studies—as to whether the association is with Alzheimer's alone, other dementias alone, or all dementias—may reflect the small numbers in the available studies.
	(F2) Feychting had 28 vascular dementia cases and 27 Alzheimer's cases. For vascular dementia, primary occupations with exposures above 2 mG conveyed an OR of 3.8 (0.65-28). For Alzheimer's, primary occupations conveyed an OR of 0.8 (0.3-2.3), and last occupations, an OR of 2.7 (0.9-7.8).	(C2) Feychting's data suggest that both conditions may be affected.

TABLE 16.2.13

SUMMARY TABLE FOR ALZHEIMER'S			
	HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:		
ATTRIBUTE OF THE EVIDENCE	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CERTAINTY?**
Chance: not an easy explanation.	Unlikely		Slight increase
Bias: in clinic-based studies might be an explanation.	More possible	Possible	No impact or slight decrease
Confounding by unspecified confounders, or shocks or contact currents.	More possible	Possible	No impact or slight decrease
Combined chance, bias and confounding.	More possible	Possible	No impact or slight decrease
Strength of association: (1) not large enough to rule out unspecified bias or confounding.	More possible	Possible	No impact or slight decrease
Consistency: four out of six studies had ORs above the null.	Unlikely	More possible	No impact or slight increase
Homogeneity: heterogeneous results by study design.	More possible	Possible	No impact or slight decrease
Dose response: not clear, in studies which had little chance of showing it.	Possible	Possible	No impact or slight decrease
Coherence/visibility: high exposure is rare so population impact would not be obvious.	Possible	Possible	No impact
Experimental evidence: no evidentiary base.	N.A.	N.A.	No impact

TABLE 16.2.13 (CONT.)

SUMMARY TABLE FOR ALZHEIMER'S			
	HOW LIKELY IS THIS ATTRIBUTE OF THE EVIDENCE UNDER:		
ATTRIBUTE OF THE EVIDENCE	**"NO-EFFECT" HYPOTHESIS**	**CAUSAL HYPOTHESIS**	**HOW MUCH AND IN WHAT DIRECTION DOES THIS ATTRIBUTE CHANGE CERTAINTY?**
Plausibility: calcium transport and immune effects evidence not strong.	Possible	Possible	No impact
No analogy.	Possible	Possible	No impact
Specificity: some confusion as to association with Alzheimer's or vascular dementia.	More possible	Possible	No impact or slight decrease

16.3 IARC CLASSIFICATION AND CERTAINTY OF CAUSALITY

16.3.1 STATEMENTS OF INDIVIDUAL REVIEWERS

REVIEWER 1 (DELPIZZO)

Degree of Certainty: The human evidence is very limited and not very consistent. This reviewer's prior is increased a little by the existence of other associations and experiments showing that EMFs can be biologically active, but the posterior level of confidence remains: "close to the dividing line of believing and not believing." For policy analysis purposes, this reviewer would use a median value of 40, with an uncertainty range of 25-55.

IARC Classification: Inadequate evidence.

REVIEWER 2 (NEUTRA)

Degree of Certainty: While there is fragmentary mechanistic evidence related to calcium transport, melatonin rhythms, etc., there is not a coherent mechanistic explanation, nor are there relevant animal pathology studies in this domain. This does not pull confidence down much below the prior degree of certainty, but it does not increase confidence either. There are two clinic-based studies, of the sort that traditionally has been considered subject to selection bias, which show associations well above the resolution power of the epidemiology. There is some weak support from an occupational study and a death certificate study. Two small population-based studies with good diagnostic criteria and job histories are not fully supportive. Taken together, the new information boosts the posterior confidence only moderately above the prior. This leaves this reviewer "prone not to believe" that EMFs increase the risk of Alzheimer's. For policy analysis, this reviewer would use a median of 20 and a range of confidence from 2 to 70.

IARC Classification: The lack of mechanistic and animal support and the heterogeneous epidemiology would lead to an IARC classification of evidence "inadequate" to characterize EMFs as a cause of Alzheimer's Disease.

REVIEWER 3 (LEE)

Degree of Certainty: The human evidence of the Alzheimer's studies is based on a small number of heterogeneous studies consisting of two clinical studies, subject to selection bias, which show positive associations; two non-supportive cohort studies; and support from an occupational and death certificate study. Overall, there is a consistently weak positive association across studies, which slightly increases this

reviewer's posterior over the prior. However, the posterior is slightly decreased by the heterogeneity of the studies, a lack of dose response, and the small number of studies contributing to the body of evidence. Hence, the posterior degree of certainty could be described as "prone not to believe" with a median of 15 and a range of 0.5 to 65.

IARC Classification: "inadequate."

16.3.2 SUMMARY OF THE THREE REVIEWERS' CLASSIFICATIONS

CONDITION	REVIE-WER	IARC CLASS	CERTAINTY PHRASE	DEGREE OF CERTAINTY FOR POLICY ANALYSIS THAT AN AGENT (EMFs) INCREASES DISEASE RISK TO SOME DEGREE
Alzheimer's				0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
	1	3	Close to dividing line	
	2	3	Prone not to believe	
	3	3	Prone not to believe	

16.4 QUESTIONS RELEVANT TO DOSE AND THE STATE OF THE SCIENCE

TABLE 16.4.1

HOW CONFIDENT ARE THE REVIEWERS THAT SPECIFIC EXPOSURE METRIC OR ASPECT OTHER THAN 60 HZ TWA MAGNETIC FIELD IS ASSOCIATED WITH THIS DISEASE?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 16.4.2

EVIDENCE FOR THRESHOLD OR PLATEAU	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 16.4.3

EVIDENCE FOR BIOLOGICAL WINDOWS OF VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 16.4.4

CONSISTENT INDUCTION PERIOD OR REQUIRED DURATION OF EXPOSURE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Feychting (Feychting et al., 1998b) showed some association of EMFs with last job while Savitz (Savitz,1998) showed somewhat more association with exposures 20 years prior to diagnosis.	None.

TABLE 16.4.5

EMFs COMPARED TO OTHER RISK FACTORS FOR THIS DISEASE	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) The associations are similar in magnitude to those with known risk factors other than the genetic factors.	(I1) Not relevant to policy, perhaps to risk communication.

TABLE 16.4.6

RELATIVE RISK COMPARED TO THAT WHICH WOULD GENERATE 1/1000 OR 1/100,000 THEORETICAL LIFETIME RISK	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Despite the late onset of Alzheimer's, the high late incidence means that epidemiologically detectable RRs translate into a greater than 1/1,000 lifetime risk, if real.	(I1) Could be of regulatory interest if true.

TABLE 16.4.7

EVIDENCE FOR RACIAL OR CLASS DIFFERENCES IN EXPOSURE OR VULNERABILITY	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
No evidentiary base.	None.

TABLE 16.4.8

ROOM FOR IMPROVEMENT IN QUALITY OR SIZE IN BEST EXISTING STUDIES	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Diagnosis, job history, exposure assessment, and sample size could be improved.	(I1) Suggest value of further study.

TABLE 16.4.9

NEW STUDIES IN PIPELINE AND ABILITY TO CHANGE ASSESSMENT	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) There are large case-control studies in California by Sobel and in Washington state by Kukel; a death certificate study by Noonan in Colorado; and a blood amyloid beta study by Noonan and Reif in Colorado.	(I1) Could modify confidence but probably not resolve uncertainty.

TABLE 16.4.10

CAPABILITY OF CHANGING ASSESSMENT	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Unlikely to resolve issue.	None.

TABLE 16.4.11

HOW LIKELY IS IT THAT FURTHER STUDIES COULD RESOLVE CONTROVERSIES?	
COMMENT AND SUMMARY	**IMPACT ON POLICY**
(C1) Better exposure assessment, in electrical jobs, including other occupational exposures such as contact currents and shocks. Larger, well funded residential case control studies, with refined exposure assessment. Such data could help resolve the question and could provide information to define exposure conditions of experimental studies. (C2) This policy-relevant disease has a small evidentiary base and would benefit from adequately funded studies.	(I1) Alzheimer's is a common condition. If it were related to EMFs, that would be important in policy formation.

16.5 CONCLUSIONS ABOUT DOSE AND THE STATE OF THE SCIENCE

16.5.1 DOSE-RESPONSE ISSUES

The evidentiary base is not sufficient to answer questions about special vulnerabilities, biological windows, thresholds, and plateaus.

16.5.2 RESEARCH POLICY

Alzheimer's becomes a common disease in the last decades of life and is devastating to patients and their families. As such, it would be an important factor in EMF policy if the degree of certainty that it caused this disease were increased. There are a number of suggestive studies. A careful exposure study of magnetic fields, electric fields, contact currents and shocks in work environments and in the residential environment, along with large well-conducted case control studies are warranted. When exposure conditions are better understood, mechanistic studies should be considered as well.