Critical flaws of the Canadian Dental Association's Review of the Richardson Report by an International Panel

Prepared by ***G. Mark Richardson, Ph.D.,***
on behalf of
the Australasian Society of Oral Medicine and Toxicology.(ASOMAT)

The major deficiencies of the International Panel Review are:

1. The CDAEP review contains numerous inconsistencies and contradictions. Their review fails to be consistent in their perspective and they even contradict their own positions stated on other pages of their review. This significantly reduces the validity and credibility of their criticisms of the Richardson report.

2. The CDAEP acknowledges the need to consider all studies when assessing the toxicity of mercury vapour and/or the risks of mercury exposure from amalgam, as done in the Richardson report and in other assessments such as by the U.S.EPA and the ATSDR. However, the CDAEP only mention a few, individual studies which support their contention that mercury vapour exposure is free of hazard and that amalgam use is risk free. Their own failure to review and consider all relevant studies, to fail to meet their own stated requirement, indicates that their comments and criticisms are not based on an informed, comprehensive evaluation of all the necessary and pertinent studies.

3. The CDAEP introduce topics totally unrelated to the Richardson report. Issues such as funding, methylmercury, and levels of mercury in blood, were not considered as part of the Richardson report. Therefore, their discussions of these issues in no way invalidate the Richardson report.

4. At no place in the entire CDAEP review do they once mention or discuss the Richardson report in the context of the risk assessment concepts, principles and practices by which it was prepared; those of Canada or the U.S., who's methods are similar to those in Canada. They only mention a few comments on risk assessment assumptions and uncertainty factors solicited from their own consultants and advisors. A credible review of the Richardson report can only be conducted in the context of the regulatory principles and practices of the agency for which it was prepared.

5. The CDAEP indulges repeatedly in unsubstantiated speculation about variables and assumptions employed in the Richardson report. Also, they are enormously speculative about potential deficiencies in the toxicological studies cited in the Richardson report. However, they repeatedly fail to cite any published studies, or to present any data, to verify their speculations. As such, their comments in these cases must be considered unsubstantiated speculation which, until the necessary research is published, in no way invalidates the Richardson report.

What follows is a point by point critique of the review of the Richardson report prepared by this international panel. This detailed tabulation makes it readily apparent that their comments and criticisms are totally without merit, lacking both validity and credibility. Their evaluation of the available literature is non-existent. They do not even acknowledge the existence of a

vast database relating to mercury vapour exposure from amalgam nor the vast database on CNS impairment due to low level mercury vapour exposure. These omissions exist despite their own claim that a thorough review of the entire database is a prerequisite to a valid evaluation of potential risks posed by amalgam and, by obvious corollary, to a valid criticism of the Richardson report. The expert panel offers only a few select citations that they claim invalidate the assessment offered in the Richardson report. However, without considering their criticisms in the context of the voluminous database on exposure and toxicity which exists, the contention that their comments and criticisms are valid is indefensible.

Members of the expert panel possess absolutely no expertise or experience in regulatory risk assessment, neither as practised in Canada nor any other national or international regulatory agency. Their entire review is undertaken with a complete lack of consideration of, or even the mention of, the common concepts, principles and practices of risk assessment as practised in Canada, or North America in general. They identified no instances where these Canadian risk assessment concepts, principles and practices were violated in the Richardson report.

Both the Health Canada policy statement on amalgam and the Dear Doctor letter, sent by Health Canada to all Canadian doctors regarding the amalgam issue, identify the Richardson report as a departmental report, available upon request to any and all interested parties. In its policy statement on amalgam, Health Canada recommends use restrictions or limitations in a variety of subgroups of the Canadian population. The adoption of the Richardson report as a Health Canada departmental report, and their recommendation of use limitations and restrictions, demonstrate that Health Canada considers the Richardson report to be valid and defensible.

Neither in its policy statement on amalgam nor in its Dear Doctor letter does Health Canada ever refer to or reference the CDA Expert Panel Review of the Richardson Report. This omission along with Health Canada's failure to conclude that the unlimited use of amalgam was a valid or appropriate policy, must be considered indicative of Health Canada's assessment of the validity and credibility of the CDAEP review.

Given their biased position and vested interest with respect to the amalgam issue, lack of regulatory risk assessment expertise, failure to acknowledge the vast database available on mercury toxicity and exposure from amalgam, and failure to couch their comments and criticisms in the context of risk assessment as practised in Canada or North America, the CDA expert panel review is no more than a political position statement of the Canadian Dental Association.

Page	Line	CDA Comment or Criticism	Response
1	10	"...acceptance or rejection of the recommendations put forward in the Richardson report."	The Richardson report made no formal 'recommendations'. It reached conclusions respecting the amount of exposure and degree of potential harm. It also estimated the number of filled teeth required to produce a dose equivalent to the proposed reference dose (TDI). However, these were not recommendations.
2	11	"Several strong critical reports have been produced by external reviewers of the original draft..."	Peer review comments must be viewed in context. Knowing that unbiased reviewers could not be identified, a balance between pro-amalgam reviewers (which were expected to criticize the report) and anti-amalgam reviewers (which were expected to laud the report) were identified and selected in order to get the best possible balance of opinion, and to get as many substantive, quantitative comments as possible, beyond simple political commentary. The original draft report was significantly revised prior to completion and release such that comments on the original draft do not apply in many circumstances, particularly pertaining to the exposure models and estimates of exposure therefrom.
3	6	"...Richardson report aims to calculate an intake level of mercury from which there are discernible health effects."	This is false. The tolerable daily intake (TDI) is a reference dose "that is believed that a person can be exposed daily over a lifetime ***without*** deleterious effect" (HC, 1994).
3	7	"... The Richardson report then calculates a tolerable daily intake for mercury from all sources and estimates the contributions from dental amalgam to the total daily intake."	The confusion of terminology in this sentence and paragraph, and elsewhere in the report, demonstrate an obvious lack of understanding or expertise in risk assessment. The TDI was calculated for mercury vapour only. This sentence suggests that the CDAEP confused tolerable daily intake with total daily intake. The TDI is the reference dose. Total daily intake is the estimated total exposure which is ultimately compared to the TDI for characterizing risks.
3	10	"...recommendations are made to limit the number of amalgam fillings."	This is false. No recommendation was made to limit the number of fillings. Such a recommendation would be part of Risk Management, not Risk Assessment. The estimate of the number of fillings required to deliver a dose of Hg vapour equivalent to the reference dose was undertaken at the request of Health Canada (included in Terms of Reference for study). The calculations were made in a manner analogous to the common practice of calculating maximum contaminant concentrations in drinking water, foods, air and soil.

Page	Line	CDA Comment or Criticism	Response
3	19-31	List of members of CDAEP	Other than Dr. B. Eley, none of the members of this panel has any expertise in risk assessment or toxicology of mercury (Vimy, 1996).
3	41-42	"...the report reflects a method and approach commonly employed for the purpose of identifying tolerable daily intakes of toxic substances..."	The CDAEP acknowledges that the methodology, at least, is common and sound.
4	1	"...but suffers from a number of short-comings which make its conclusions unjustifiable."	Richardson disagrees. The study has stood the test of publication following peer review, and is a departmental report distributed by Health Canada as part of its package of information on amalgam.
4	7-16	"...it has been pointed out by Lipfert et al. (1994) that "the maximum risk developed from such probabilistic methods is an unstable statistic which can vary greatly from trial to trial; furthermore, the maximum predicted risk will increase with the number of realizations in each trial. ... based upon 5000 trials (Lipfert et al., 1994, page 9)."	It is true that the maximum value in a probabilistic model is unstable. However, the mean or average value, its standard deviation and all percentile values between at least the 5th percentile and the 95th percentile are very stable after about 5000 trials of the model. The Richardson models were run for 10,000 trials, thus ensuring the stability of the most important output statistics, the average, standard deviation and percentiles. All conclusions of the Richardson report were based on average output values of the models, not on maxima.
4	17-18	"It is clear that without sufficient volumes of data such an analysis is very questionable."	The quote taken from Lipfert et al. related to their suggested minimum number of repetitions of the model to generate valid, stable output, not to the volume of input data. The CDAEP implies the opposite which is not true. Certainly, Lipfert et al., to whom Richardson contributed data on certain input variables that they could not obtain from any other source, did not mean this interpretation. The point being made by Lipfert et al. in the quote listed by the CDAEP in lines 13-16 is that the model must be reiterated (repeated) enough times that the full distribution of each random exposure variable in the equation is adequately sampled in order to be representative of its entire distribution (range). The number of repetitions suggested by Lipfert et al. was 5000. The Richardson models were run for 10,000 iterations.

Page	Line	CDA Comment or Criticism	Response
4	19-20	"The Richardson report also employs Monte Carlo statistical methods for random sampling the input data."	True, this was the study Richardson was asked to conduct. It is the same type of study as conducted by Lipfert et al. on Hg exposure due to coal combustion, a study from which the CDAEP quotes and thus must consider valid.
4	20-23	The use of the Monte Carlo statistical method is not an adequate substitute for actual direct clinical measurements such as those reported in this review by the international panel using data from Berglund (1990) and Berglund and Molin (1996)."	All published clinical studies of Hg exposure and effects relate to only a few people (100 at a maximum). Monte Carlo methods were required to generate statistics for the entire Canadian population with amalgam (>15,000,000) a population too large to be evaluated clinically. The only clinical studies which quantitatively measure the dose to mercury from amalgam is by Skare and Enqvist (1994). The studies of Berglund (1990) and Berglund and Molin (1996) do not clinically measure mercury exposure in an adequate mass balance approach. Skare and Enqvist (1994) undertook a complete mass balance analysis of Hg entering and leaving the body by all routes in a small group of patients. This is the only study of its kind.
4	23-25	"In addition, the use of the Monte Carlo simulation method may be questionable for data that are not based on truly independent events such as eating, swallowing, breathing, etc.	This is not true. Monte Carlo methods can be applied to data that are dependent (related). However, the degree of dependence (correlation) between such variables must be quantified, but only for variables that have a correlation coefficient of 0.5 or greater (Smith et al. 1992). Such a strong correlation does not exist with the variables employed in the Richardson models.
4	26-29	The interpretation and use of the uncertainty factors in the Richardson report is not conventional, since an uncertainty factor of 10 is in general only applied when moving from a lowest adverse effect level (LOAEL) based on a CLINICAL effect to a no observed adverse effect level (NOAEL)."	This is not true. LOAEL to NOAEL adjustment is routinely a factor of 10 for 'significant' effects whether clinical or sub-clinical. CNS impairment is considered significant. See guidelines published by U.S.EPA and U.S.ATSDR for further confirmation of this point. The measurement of hand tremor (in the Fawer et al. study) was measured clinically with equipment designed for that purpose. Therefore, the CNS effect is considered 'CLINICAL".

Page	Line	CDA Comment or Criticism	Response
4	29-31	"Further, as illustrated in the body of this critique, some input variables are highly questionable and in some cased incorrect."	This is a sweeping generalization which is, in fact, incorrect.
4 5	32-36 1-3	"Another major shortcoming ... Such information was available to reviews such as the CCEHRP report of 1993 which represents a thorough and comprehensive evaluation with input from a large number of scientists."	The CCEHRP report clearly states that "This report is not intended to serve as the authoritative source on dental amalgam safety,..." (CCEHRP, page viii). Therefore, it is not comprehensive as stated by the CDAEP. The CCEHRP report clearly states that "nonetheless, the possibility that this material, as well as currently available alternatives, could pose health risks can not be totally ruled out because of the paucity of definitive human studies." (CCEHRP, page x). Therefore, CCEHRP could not determine that amalgam is absolutely safe, as implied by the CDAEP. The CCEHRP clearly states "Most data suggest that the daily mercury dose is 1 to 5 ug higher for subjects with 7 to 10 amalgams than for persons with no amalgams." (CCEHRP, page III-29). For persons with 25 amalgams (the reported maximum in Canada), the CCEHRP report would indicate a daily dose range from 1 to 12.5 ug (2.5 X 5 ug). The daily dose range for adults with from 1 to 25 filled teeth was estimated in the Richardson report to range from 0.2 to 11.6 ug/day, virtually the same as estimated by CCEHRP. Therefore, CDAEP criticism of the validity of the Richardson report, based on the findings and conclusions of the CCEHRP report, are totally without merit. The CCEHRP and Richardson reports are complementary, not contradictory.
5	4-6	"Comprehensive and objective review requires... the Richardson report was prepared by a single researcher..."	Comprehensive risk assessments are routinely compiled by a single individual and then submitted for extensive peer review to ensure the validity of models, citations, conclusions, etc. This was the approach taken for the Richardson report. The CDA has published in its Journal a review of dental amalgam by a single author who cited only 46 references. By the CDAEP's comments it must be concluded that the CDA has published an invalid and unobjective (i.e., biased) review in its own journal.

Page	Line	CDA Comment or Criticism	Response
5	6-9	"...who prior to the completion of the report was quoted..."	The quotes attributed to Richardson by the CDAEP (from the Calgary Herald) are not quotes but were the headline of the article and a statement made in the body of the article by the reporter. At no time were these statements made by Richardson to the press. The reporter came to these conclusions after hearing a description of the study terms of reference and methods.
5	10-13	"Although extensive peer review was acknowledged in the Richardson report, the acceptance and incorporation into the report of comments and criticisms of reviewers was not subject to external scrutiny."	The CDAEP implies that 'peer review of the peer review' was required. This is silly. An extensive body of peer review comments was received (total volume of review comments exceeded length of report) and a tabulation of all comments was prepared along with the suggested response (revisions, changes to calculations, no revisions, etc.) to each comment. This was submitted to Health Canada Management who approved the suggested revisions (or no revisions, depending on each comment) prior to completion of the final report. It would be unique to have external 'peer review of the peer review'.
5	14-16	Finally, as illustrated within the body of this critique, many of the input variables in the Richardson report and the interpretation of research data from the literature raise very serious concerns."	Indeed, they raise serious concerns for the CDA, who present a very biased and incomplete interpretation of the published literature.
5	19	"The review of the literature ... is superficial..."	The literature review conducted in the Richardson report is the most thorough and exhaustive of any report dealing with mercury exposure from amalgam. The report included a total of 212 citations. This compares to only 119 cited in Appendix III of the CCEHRP report (this is the only section of the report which deals with assessment of mercury exposure). A paper in the CDA's own journal entitled "Dental Amalgam: Toxicological Evaluation and Health Risk Assessment" (M. Levy, CDA Journal, volume 61, no. 8, 1995), purportedly an authoritative treatment of the subject, included only 46 citations.

Page	Line	CDA Comment or Criticism	Response
5	22	"The probabilistic analysis has made use of input variables which are inappropriate and in some cases inaccurate."	This has two aspects: 1) the mathematical models; 2) the probabilistic treatment. The mathematical models were thoroughly scrutinized by 17 peer reviewers on behalf of Health Canada and by a further three peer reviewers on behalf of the journal in which it is published. Substantive comments resulted in revisions prior to report completion and peer-reviewed publication. By and large, peer reviewers considered the models to be valid, defensible and thorough. Independently from my efforts, Weiner and Nylander (1995; An estimation of the uptake of mercury from amalgam fillings based on urinary excretion of mercury in Swedish subjects. Science of the Total Environment, volume 168, pages 255-265) estimated exposure to mercury from amalgam employing the same approach to dose estimation as Richardson employed. Their paper was also peer-reviewed and published. This further validates the general approach which Richardson used to estimate mercury exposure. The probabilistic treatment was the first of its kind employed in Canada (or anywhere for that matter) to address a regulatory issue of chemical exposure. It employed the best data available. Peer review by persons expert in probabilistic assessment found the analysis to be thorough, valid and defensible. The results of the Richardson models agree almost exactly with the estimates of exposure presented in the CCEHRP report from the U.S. Public Health Service, the report which is cited by the CDAEP as 'the' authoritative risk assessment. Results of the Richardson models also agree well with estimates of exposure published by the World Health Organization (1991), those of Weiner and Nylander (1995), Skare and Enqvist (1994), among others. Therefore, the models and their estimated exposures do not seem to be in doubt.

Page	Line	CDA Comment or Criticism	Response
5	24	The calculations in the Richardson report of the Tolerable Daily Intake (TDI) are ... dominated by the interpretation and the selection of the mercury in air value from the key reference paper (Fawer et al. (1983)).”	Richardson does not understand why this is a key concern. This is, in fact, how tolerable daily intakes (Health Canada), reference doses (U.S.EPA) and minimum risk levels (ATSDR) are established. To complete a risk assessment, exposure must be compared to some benchmark of known or anticipated safety. TDIs, RfDs and MRLs are those benchmarks of known or expected safety against which estimated exposures are compared to determine if potential human health risk exists. This is the essence of regulatory risk assessment. It is also worth pointing out that the U.S.EPA and the ATSDR also both use the Fawer et al. (1983) study for the determination of reference exposure levels. In fact, Richardson accepted the advice of the key author of the 1994 ATSDR Toxicological Profile for Mercury (Richard Canady; he was one of the selected peer reviewers) to use the Fawer study rather than another one which Richardson originally favoured (Ngim et al. 1992; for reasons of sample size, good representation of both genders and because dentists were the subject population).
5	28	“It is clear that conversion of data for mercury in air to values for mercury in urine is not a simple process. Yet in spite of this the Richardson report made use of this as a essential key step in order to produce a TDI.”	This is not true. The derivation of the TDI had nothing to do with mercury levels in urine. The TDI was derived from the average room air concentration, considering breathing rate, duration of exposure (8 hours per day; 5 days per week), absorption rate (80%) and adult body weight (70 kg). Based on this statement, Richardson is uncertain as to the Panel’s grasp of my report or of risk assessment in general. Richardson suspects what the Panel might be referring to is the method used to convert urinary Hg levels associated with amalgam fillings to an exposure dose. This did involve this step. However, this has nothing what so ever to do with the derivation of the TDI. This ‘conversion’ was peer-reviewed and accepted for publication by Richardson and independently by Weiner and Nylander (1995). The estimates of exposure produced by this ‘conversion’ are virtually the same as those of the CCEHRP report and WHO. Therefore, the validity of the calculation does not seem to be in doubt.

Page	Line	CDA Comment or Criticism	Response
5	31	"The dental epidemiological data used in the report is grossly out of date."	The data were collected in 1972 as part of the Nutrition Canada Survey of approximately 13,000 Canadians. There are no other national epidemiological data on dental health status (including numbers of filled teeth) in Canada. However, comparison to more recent Canadian data for 13 year olds, and to U.S. data from 1986, indicates that the data are still representative. Data for numbers of filled teeth for 13-year-olds were in reasonable agreement with various provincial data from 1980 to 1985. Based on the most recently published Canadian statistics for 13-year-olds (the only age group consistently reported), the average numbers of filled teeth were: 2.3 in Alberta in 1985 (Lizaire et al. 1987); 4.45 in Quebec in 1984 (Payette et al. 1988); 3.83 in B.C. in 1980 (Hann et al. 1984); and 2.6 in Ontario in 1984 (Johnston et al. 1986). Unpublished data for this same age group, collected as part of the NCS, indicated an average number of filled teeth for all surveyed 13-year-olds (n=358) of 2.54, which is comparable to the more recent statistics. The average numbers of filled teeth in the adult U.S. population in 1985-86 was 9.05 (USDHHS 1987), a number comparable to the 8.23 filled teeth, on average, for Canadians aged 18 to 102 years with filled teeth (NCS, unpublished data). Therefore, the NCS data were employed to define this variable for all age groups. It should be noted that the estimation of the number of fillings required to produce an exposure equivalent to the TDI is independent of data on the numbers of filled teeth in the population.

Page	Line	CDA Comment or Criticism	Response
6	2	"The key reference study by Fawer et al. (1983)... the pre-clinical symptoms observed are likely to be related to past history."	It is true that the Fawer et al. study did not present dose-response information. However, this can not be viewed as a barrier to its application to derive a TDI. The weight of evidence is overwhelming that neurological effects are seen at mercury levels of 0.026 mg/m3 of air and lower. This weight of evidence is reviewed in my report and is also discussed by the U.S.EPA in their document supporting their reference air concentration for mercury vapour (found in the Integrated Risk Information System (IRIS) accessible on the Worldwide Web). Also, the U.S.EPA and ATSDR both applied the Fawer study to derive reference exposure levels. The statement that "the Fawer et al. (1983) study made no claim linking the hand tremor to the mercury in air values" is absolutely ridiculous. The link is made in the title to the study for heaven's sake (Measurement of Hand Tremor Induced by Industrial Exposure to Metallic Mercury", Fawer et al., 1983). The symptoms reported in the Fawer study may have a link to past history. Studies have shown a relationship of neurological impact to average mercury exposure level, to duration of exposure and to the incidence of peak exposures. However, dental patients have long duration of exposure and are subject to peak exposure events, for instance when amalgams are removed and/or inserted. Therefore, this potential relationship of effects in the Fawer study group to 'past history' does not preclude it from being relevant to the dental situation.
6	12	"The 'Hand Tremor' test employed ... was not one of the twelve tests selected for..."	So what? Regardless of this comment, the weight of evidence that low level mercury vapour exposure causes neurological effects is over-whelming. Numerous studies have measured CNS impacts in numerous ways, with the vast majority demonstrating measurable impairment.
6	15	"The proposed tolerable urine concentration (TUC) of 0.7 ug/L is very unrealistic since it is exceeded in many amalgam free individuals."	It is exceeded by some, but not many amalgam-free individuals. The general levels reported for the vast majority of amalgam-free individuals appears to be less than or equal to 0.5 ug Hg/L urine. Regardless, the level of mercury in the urine of people with no amalgam has nothing to do with the establishment of a toxicological benchmark. Many people exceed the toxicological benchmarks for dioxins, PCBs and other contaminants, but this does not invalidate the benchmark. What it does (or should do) is raise questions as to where or from what those individuals are being exposed (i.e., what source if not amalgam?)

Page	Line	CDA Comment or Criticism	Response
6	17	"The key paper used in the Richardson report...(Skare and Engqvist, 1994) should not be used..."	Richardson totally disagrees. The paper by Skare and Enqvist was the most recent, quantitative analysis of baseline (unstimulated) Hg release rate available, and still is. Yes, the rates were higher than those preferred by the CDA Expert Panel, but the detail and effort made to make accurate measurements was the best published to date.
6	25	"The average chewing magnification factor..."	The preponderance of data used to establish the 'chewing magnification factor' were based largely on data relating to gum chewing. The vast majority of studies examining the increased emission of Hg following chewing used gum as the basic 'food'. Therefore, our choice of data on this issue was limited due to the nature of the database of published studies. However, The values of the stimulation factor incorporated the values reported in the Berglund study, the preferred study of the CDA Panel.
6	31	"The stimulation magnification factor obtained almost exclusively from gum chewing should not have been used in the Richardson report for tooth brushing stimulation."	No data have been put forward that indicates that the stimulation caused by brushing will cause a lesser or greater degree of increased Hg emission than caused by abrasion due to chewing.
7	1	"The magnification factors used in the Richardson report need to be significantly reduced..."	This is a repeat and extension of items previously discussed.
7	7	"The Richardson model assumed maximum mercury (stimulated) release from ..."	The studies Richardson cites demonstrated an almost instantaneous increase in mercury emission, followed by exponential decline once stimulation ceased. This is how the effect was modelled.
7	10	"The choice of the reference paper used for conversion from the number of tooth surfaces restored with dental amalgam to the number of amalgam filled teeth...is inappropriate."	No data has as yet been presented to more accurately quantify the number of amalgam surfaces per filled tooth other than the data we used.

Page	Line	CDA Comment or Criticism	Response
7	16	"... the same average number of amalgam surfaces per amalgam filled tooth..."	Again, no other quantitative data were available to better differentiate between age groups in relation to number of restored surfaces per amalgam filled tooth.
7	22	"Regression plots of the total number of amalgam surfaces versus mercury exposure...."	This comment is correct. Richardson applied a safety factor of 100 to the average dose received by the Fawer et al. subjects to determine my TDI. The number of filled teeth required by an adult to receive a dose equivalent to the TDI was 4 filled teeth. Therefore, it is not a far stretch to determine that it would require 400 teeth to receive the same dose experienced by the Fawer subjects. However, the dose received by the Fawer subjects produced clinically detectable tremor. It was a requirement of my terms of reference to determine a dose which should be free of deleterious effect for the vast majority of the population. Obviously, that 'reference' dose (TDI) has to be less than the dose received by the Fawer subjects in order to be free of clinically diagnosable hand tremor.
7	28	"The scientific literature does not contain any study which links mercury released from dental amalgam fillings and an observable adverse clinical effect which can be used to calculate a TDI."	This is true, but no study has yet been conducted to measure sub-clinical CNS effects (cognitive function, hand tremor, etc.) in dental patients with amalgam compared to dental patients who never had amalgam. Therefore, it is necessary to resort to other studies of mercury exposure. Remember: mercury is mercury is mercury, regardless of the source. Mercury from amalgam is no safer than mercury from workroom air, if exposure level is the same. Even the CCEHRP report indicates that "there are no scientifically acceptable studies with sensitive, standardized measurements for physiological and behavioral changes in non-occupationally exposed populations,..." (CCEHRP, page III-29). Therefore, it is necessary to rely on occupational studies of Hg exposure to deduce a TDI. This was done in the Richardson report, and by the U.S.EPA and the U.S.ATSDR.

Page	Line	CDA Comment or Criticism	Response
8	1-9	"The panel noted that a very recent study by Berglund and Molin (1996)..."	Regarding the Berglund and Molin (1996) study, the fact that self reported illness does not relate to amalgam fillings is no surprise and is not a significant basis for criticism of the Richardson report. Of more interest is the recently published article from Echeverria et al. (1998), and a companion article in press in the FASEB journal, which demonstrates a dose-response relationship between CNS effects and mercury exposure in the same range as experienced by dental patients with amalgam. That study, conducted on dentists (and, therefore, the mercury arises from amalgam) further demonstrates that CNS effects are likely measurable at levels of exposure observed in the general population with amalgam fillings.
8	10-18	The calculated daily intake of inhaled mercury vapour,...,was less than 5% of the daily uptake calculated at the lower concentration range given by WHO (1991), at which subtle symptoms have been found in particularly sensitive individuals."	The WHO (1991) is cited out of context and inappropriately. First, the document was published in 1991 and the most recent citations date only to 1990. The CDAEP was critical of the Richardson report not including a 1996 reference. Second, the WHO document did not include all of the recent occupational literature which repeatedly demonstrates CNS impairment at levels of exposure well below 25 ug/m^3. Third, the WHO report states that "Appropriate epidemiological data covering exposure levels corresponding to less than 30-50 ug mercury/g creatinine are not available." This indicates that the conclusion extrapolated by the CDAEP is invalid and can not be attributed to WHO as done. Fourth, The WHO report states that "A consequence of an immunological etiology is that, in the absence of dose-response studies for groups of immunologically sensitive individuals, it is not scientifically possible to set a level for mercury (e.g., in blood or urine) below which (in individual cases) mercury-related symptoms will not occur." This suggests that, contrary to the CDAEP's interpretation, the WHO has not established a "daily uptake at which subtle symptoms have been found in particularly sensitive individuals." Finally, the WHO states that "the results of the few epidemiological studies [of amalgam bearers] produced are inconclusive." Therefore, citation of the WHO report to suggest that such studies are conclusive with respect to amalgam safety is inappropriate.

Page	Line	CDA Comment or Criticism	Response
8	19-24	"The panel would suggest that studies of this type..."	The CDAEP does not define what it means by "studies of this type". It can not be ascertained what type of study they are referring to. The WHO report was a literature review, not an epidemiological study. It is agreed that broad epidemiological studies of CNS impairment (cognitive function, etc.) in persons with amalgam versus those without amalgam is warranted and required, as suggested in the Richardson report.

Page	Line	CDA Comment or Criticism	Response
9	1	"The Richardson report is not an official report of Health Canada"	This is false. In the Health Canada policy statement and in the 'Dear Doctor' letter, the Richardson report is clearly identified as a departmental report, and is distributed by the Department free of charge to anyone requesting it.
9	2	"... not a policy document..."	This is correct. However, it was not intended to be a policy document but rather a technical report to be considered when policy was formulated.
9	3	"The report does not provide data on the exposure of the Canadian population to mercury from food or from amalgam fillings..."	This is false. The report is considered the most up-to-date and complete determination of mercury exposure from all sources (amalgam, food, air, water, soil) in Canada.
9	4	"... since reliable up to date data on mercury in Canadian food (other than fish)..."	The data used are reliable and up to date. Although not Canadian data, Canada and the United States share a common North American commercial food base. The data employed were from up to date market basket surveys from the U.S.FDA and the sources of those foods (local, regional, national, imported) are the same sources from which Canada obtains commercial foods.
9	5	"...epidemiological dental data are not available."	This is incorrect. Extensive evaluation of the Canadian dental data was undertaken to demonstrate it relevance. As discussed in the report, the data employed agreed with recent U.S. population statistics, and data for Canadian 13 year olds were consistent with more recent Canadian data.
9	7	"...based entirely on existing information which has been out in the scientific literature for a considerable number of years."	The risk assessment relied on published literature. However, literature up to 1995 (the year the report was undertaken) was incorporated. This is the most up-to-date published assessment of mercury exposure and risks available.

Page	Line	CDA Comment or Criticism	Response
9	8	"It does not generate any new data or information."	On the contrary, it is the most original treatment of the issue available. Among other things, new data and information include: a) quantification of exposure to mercury from amalgam (and other sources) for the Canadian population; b) the relative contributions to exposure from amalgam, food, air, water and soil; c) quantification of the proportion of the Canadian amalgam-bearing population which exceeds the proposed reference dose (and the data can be used to determine the proportion of the population which exceed any other specified level of exposure); d)determination of the number of fillings necessary to produce, on average, a dose equivalent to the reference dose. If the data were not original or new, publication in a peer-reviewed journal would not have been possible. New and original work is a requirement of publication in credible science journals.
9	9	"Many of the referenced data are 15 to 25 years old."	Age does not matter if the data are reliable, valid and still pertinent to the issue. This was the case with all data employed in the Richardson report.
9	10	"The key reference paper used for calculating the TDI is 12 years old.	This is true. However, it is consistent with numerous more recent studies of CNS effects due to mercury vapour exposure and is considered the best reference upon which to establish a reference dose. The same conclusion was reached by the U.S.EPA and the U.S.ATSDR.
9	11	"The recommendations are based on ..."	No recommendations were presented in the report. The conclusions were based on the results of a detailed analysis which incorporated theoretical analysis and probability theory, which is routine and necessary when the exposed population numbers in excess of 15,000,000. Federal departments of statistics, public opinion surveys, etc. generate vast databases for 'representative samples' of the population from which very accurate projections of population characteristics can be deduced. The methods used in the Richardson report are no different.

Page	Line	CDA Comment or Criticism	Response
9	20-23	"The overall conclusions of ... is that the amount of mercury release from dental amalgam is below a toxic threshold however a small number of toxic reactions have been reported."	This is false. The U.S.ATSDR identified amalgam-bearers as a potentially at risk population because exposure, although not quantified, was stated to exceed the ATSDR chronic MRL for mercury vapour. The CCEHRP report clearly states that "nonetheless, the possibility that this material, as well as currently available alternatives, could pose health risks can not be totally ruled out because of the paucity of definitive human studies." (CCEHRP, page x). The CCEHRP report also states that "there are no scientifically acceptable studies with sensitive, standardized measurements for physiological and behavioral changes in non-occupationally exposed populations,..." (CCEHRP, page III-29). Therefore, CCEHRP did not determine that exposure from amalgam is "below a toxic threshold" as stated by the CDAEP. Likewise, the report of the Swedish National Board of Health has been misquoted and misrepresented. It should also be noted that the Swedish government has recently (April 1998) released a further examination and analysis of this issue which suggests that the exposure from amalgam is not risk-free.
9	26	"...why are we only now able to calculate a TDI?"	The derivation of TDI's is driven by regulatory requirement. Until 1995, Health Canada did not require a TDI for mercury vapour exposure and, therefore, had not bothered to develop one. The U.S.EPA and the ATSDR, however, had published reference exposure levels for mercury vapour many years earlier, as required by their environmental legislation.
9	27	"International experts agree that it is not possible to calculate an acceptable TDI for mercury derived from dental amalgam based upon the present data and knowledge status."	This is false. Richardson has seen no statement of experts to this effect, other than from the CDAEP. The TDI is for mercury vapour and is not specific to amalgam. Mercury is mercury is mercury. The mercury from amalgam is no different, nor will it elicit different effects, from the mercury vapour from any other source. What will vary is the amount of exposure from the different sources of mercury vapour and this is why the Richardson report was required; to quantify mercury exposure from amalgam versus other sources in order to compare these exposures to a reference level (TDI).
9	29	"Recognizing the fact that the Richardson report used the formula developed by Olsson and Bergman (1992)...	This is incorrect. The general approach of Olsson and Bergmann (1992) was accepted as one valid method to derive exposure. However, the technical detail of the formula employed in the Richardson report far eclipsed the simple treatment afforded by Olsson and Bergmann.

Page	Line	CDA Comment or Criticism	Response
9	32	"... there is a lack of reliable parameters for numbers to be inserted into the model equation."	This may have been true in 1992. However, there was a very good database of reliable data for determining values for equation variables when we undertook the study in 1994/95. These are described in explicit detail in the Richardson report.
9	34	"The question 'How dangerous are dental amalgams? must be based on reliable dose values determined accurately and independently."	The Richardson report did just that. Two independent models were developed to derive exposure knowing that if the estimates of the two models differed markedly then the exposure estimates were obviously questionable. The estimates derived from the two independent models (developed by two independent risk assessors physically separated by about 2,000 km) were within 10 to 20% agreement, which is excellent. Also, the estimates of exposure in the Richardson report are in virtually total agreement with the estimates derived in the CCEHRP report and agree well with those of WHO (1991), Skare and Enqvist (1994), among others. Therefore, the exposure estimates are reliable and accurate, as evidenced by the growing body of literature and reports which indicate exposure ranging up to between 12 and 17 ug/day for individuals with up to 25 filled teeth, the apparent maximum (at least in Canada).
9	37	"They clearly state: '...'"	A large (and growing) volume of data on mercury in urine and faeces now exits. There is also good agreement from several independent analyses of the levels of mercury exposure arising from amalgam. Therefore, the time for correlation studies to determine the degree of mercury exposure from amalgam fillings has arrived, if not already completed and past.
10	3-7	"The WHO publication.. States: "Both the predicted mercury uptake from amalgam and ... difficult to make accurate quantitative estimates of mercury release and uptake by the human body from dental amalgam tooth restorations."	This is not true. The primary reason that probabilistic methods of risk assessment were used was to account for human variability in the numerous exposure factors. Biological systems, such as the human body, are inherently variable. This has a genetic basis as well as factors related to health status, behaviour, etc. Only probabilistic methods of risk assessment, as used in the Richardson report, permit the inclusion of the full range and frequency of values for the myriad exposure factors to be considered such that the variability in exposure across a population can be quantified (Richardson, 1996). This human variability makes it difficult to estimate exposure on an individual basis, but probabilistic methods generate accurate estimates on a population basis. Just as it is difficult to predict if an individual will be struck by lightning, the proportion of the population that will be struck by lightning can be accurately predicted.

Page	Line	CDA Comment or Criticism	Response
10	9	"The initiative of the Richardson report..."	The Richardson report was prepared as a result of correspondence from the Minister of Health in Ontario to the federal Health Minister.
10	14	It is indeed a sad state of affairs...	It was beyond the scope of the project to criticize the policy decision to commission the Richardson Report.
10	16	"...rather than requesting the sound scientific advice of international and national experts..."	This is exactly what the federal minister did in response to receiving the letter from the Ontario Minister of Health. A national expert on mercury and on exposure assessment (Richardson) was asked to advise the federal Minister and his senior bureaucrats as to the exposure and risks related to dental amalgam. It is interesting to note that the Ontario Dental Association was also asked by the Ontario Minister of Health to comment on the issue of dental amalgam safety. The ODA cited the magazine "Consumer Reports" as an authoritative source of health information. Richardson does not mean to malign a popular and valuable consumer information publication, but it can hardly be considered a reliable or authoritative source of information on the potential risks of mercury exposure from dental amalgam.
10	19	"It should be noted that..."	This seems to be a misplaced complaint about lack of funding from government to the CDA and does not belong in what is supposed to be a scientific evaluation of the Richardson report. However, it does underscore the political, rather than scientific or technical, purpose of the CDAEP report.
10	27	"...Firm (and scientifically sound) guidelines on the use of dental amalgam cannot be produced without more accurate information on release of mercury from dental amalgam and on the toxicity of low concentrations of mercury".	This is why Health Canada commissioned the Richardson report; to review the available information, to determine accurate estimates of exposure, to establish a TDI based on the large and increasing weight of evidence for CNS impairment due to low concentrations of mercury. The data from the Richardson report were employed, along with other inputs, to develop Health Canada's guidelines (policy) on amalgam use.
11	6	"The report was essentially a review of the scientific literature..."	A review of the literature was a necessary aspect of the study. However, a detailed and technical risk assessment was also undertaken, using methods which the CDAEP itself has acknowledged as being valid.

Page	Line	CDA Comment or Criticism	Response
11	9	"...seconded from Environment Canada."	This is false. Richardson was an employee of Health Canada and was head of a unit responsible for risk assessment related to contaminated soil and hazardous waste sites prior to being asked to undertake the risk assessment on dental amalgam.
11	10	"...he took a year to do so.'	The first draft was completed in approximately 8 months and the final report was completed in 11 months. These deadlines were dictated by departmental requirements.
11	10-38	"Mark Richardson presented a poster..."	This appears to be a critique of a poster Richardson presented at a mercury conference in Arkansas in late 1994. The poster presented the preliminary work in support of the risk assessment of dental amalgam and need not be further discussed as the Richardson report presented the final analysis of this exposure.
12	7-26	From Calgary Herald...	Note that Richardson was never quoted as saying that he expected to recommend a limit on the number of fillings. In the interview with the reporter Richardson had, however, indicated that the information on exposure, when combined with the TDI, could be used to derive the number of fillings needed to produce a dose equivalent to the TDI and that that information could be used to derive a limit if exposure exceeded the TDI. Note that in the past few pages the CDA Expert Panel has abandoned its purported expert review of the technical and scientific nature of the Richardson report and is presenting political commentary and positions on the issue. This likely reflects the true 'expertise' of the CDAEP.
13	1-17		More political commentary. No comment
13	19	"Determining body burden in human subjects is however, considerably more difficult. The problem is also further confounded..."	The Richardson report did not estimate body burden, it estimated exposure. These are two distinct quantifications, the difference of which is obviously not apparent to the CDAEP. The issue of fish consumption is a red herring here. Not only did the Richardson report differentiate the sources of mercury exposure (amalgam, food (including fish), air, water, soil) it also differentiated the different forms of mercury (methyl, ionic, vapour) and corrected for the differential absorption of these different forms by the different routes of exposure (inhalation versus ingestion).

Page	Line	CDA Comment or Criticism	Response
13	23	"At the meeting with the CDA committee Dr Richardson refused to discuss..."	This is incorrect. Before Richardson had a chance to even discuss the methods used for the analysis, the committee unanimously (and loudly) claimed that the study as "unscientific". This was perplexing since the group was supposed to be composed of 'objective' scientists who should not have pre-judged the report or its methods even before they had seen it or heard a description of its methods. As they were unwilling to listen to the presentation, Richardson departed, leaving Dr. Philip Neufeld of the Bureau of Medical Devices to discuss the politics of the issue with the CDA. The list of key research papers used in the Richardson report was, in fact, left on the overhead projector at the CDA meeting at the time of my departure.
13	29	"This unapproved document..."	The Richardson report was approved by Health Canada and released by the department.
13	29-32	"... suggested that a maximum limit of four amalgam restorations..."	The calculation related to the number of amalgam fillings required to produce a dose equivalent to the TDI. Risk management actions, such as implementing limits, was not a function of the Richardson report and, in fact, at no time has Richardson proposed such a limit as a risk management step.
13	33-34	"...to publish misleading figures such as this is unacceptable."	This is incorrect. Health Canada routinely publishes risk assessments which quantify exposure, characterize risks and propose limits on exposures arising from foods, air, water and soil. Richardson simply applied standard, routine methods to determine what degree of exposure, in terms of the number of amalgam-filled teeth, constitute a dose equivalent to the TDI. However, as with guidelines for drinking water, numerous other factors are considered prior to establishing exposure limits and the eventual risk management strategies, such as concentration or exposure limits. Such risk management guidelines or limits will often result in exposure in excess of the TDI. Arsenic is a good example. In Canada, drinking water guidelines are routinely derived such that the TDI, or a cancer risk of 1 in 100,000 (if the substance is carcinogenic) is not exceeded. In the case of arsenic, because of limitations in the ability of drinking water treatment methods to remove arsenic, the Canadian drinking water guideline is associated with an estimated cancer risk of 1 in 1,000. The supporting document presents the analysis of risks and describes the concentration of arsenic in water associated with a cancer risk of 1 in 100,000. The Richardson report is analogous to this.

Page	Line	CDA Comment or Criticism	Response
13	34	"The TDI is set so low as to make it completely meaningless."	On the contrary, the calculated TDI has proved very meaningful. By contrast, the MRL published by the U.S.ATSDR is about 5 times lower than the TDI proposed in the Richardson report.
13	35-38	"It is highly questionable to use a value which is half the level of the internationally agreed safety threshold limit value (TLV)..."	No such 'internationally agreed" TLV exists. Published, international occupational limits for mercury vapour range from 5 to 150 µg/m^3 (IARC, 1993). The limit published by the ACGIH (1997) is 25 µg/m^3, the average level of exposure reported for the subjects of the Fawer et al. study. Also, occupational limits were established to prevent proteinurea, which is a biomarker for (reversible) kidney damage. Most studies investigating CNS effects due to occupational mercury exposure conclude that the current occupational limit does not protect against CNS impairment. It should also be noted that occupational limits are established for a healthy, predominantly male subpopulation, and that these limits have never been viewed by regulatory agencies as an acceptable basis for policies respecting the general, non-occupational population, which reflects a wider range of susceptibilities to chemical exposures. Public health risk management strategies respecting chemical exposures are seldom, if ever, based on occupational TLVs.

Page	Line	CDA Comment or Criticism	Response
14	2-5	"The review of literature in the Richardson report tends to be rather superficial..."	This is false. The Richardson report presents the most extensive review of literature available in the published literature. A total of 212 references were cited, compared to 119 in the CCEHRP report, for example.
14	6-17	"On page 1, the paper by Englund et al. (1994) is referred to in connection with removal of amalgam fillings. This is not correct..."	The citation as made in the Richardson report is correct, and did not refer to amalgam removal. Appropriately, the Richardson report states: "...the remission or elimination of effects following amalgam removal has been attributed to placebo effect (Englund et al., 1994)." The Englund et al. (1994) paper is entitled "DMSA Administration to Patients with Alleged Mercury Poisoning from Dental Amalgam: A Placebo-Controlled Study" (J. Dent. Research, 73(3): 620-628). This study reported that reduction in mercury body burden did not alleviate symptomology (keep in mind that the study was small (n=20), of short duration and statistically weak, as acknowledged by the authors). This study has been cited by others as evidence that reducing the body burden of mercury (by amalgam removal which would also reduce mercury body burden) is not associated with the alleviation of symptomology and that any improvement must be placebo effect. This was the nature in which it was cited in the Richardson report, not that it was a study of amalgam removal, per se.
14	18-35	"...the Richardson report then goes on to mis quote and distort the result from another paper dealing with excretion of mercury using chelating agents. ..."	The CDAEP presents a quote from the Richardson report and a quote from the citation (Aposhian et al., 1992). Richardson fails to see the difference between his interpretation and that of the authors. Further, the CDAEP cites the value of 66% of human body burden of Hg was derived from amalgam. 66% is equivalent to two thirds. Post-chelation urinary Hg levels correlate with body burden. If 66% (two thirds) of the post-chelation, excretable mercury in urine is attributable to amalgam fillings, as indicated by Aposhian et al., then where is Richardson's error? It is obvious that the data as quoted in the Richardson report is not in error as suggested by the CDAEP.

Page	Line	CDA Comment or Criticism	Response
14 15	36-38 1-14	"In the second paragraph ... the authors have not studied effects of the intensity and duration of stimulation. ... The Richardson report seems to have misunderstood the content of the papers by Svare et al. (1981) and Berglund (1990). ..."	The paper by Berglund (1990) shows differing rates of Hg emission due to different meals and snacks (cup of coffee + white bread roll; Wiener schnitzel with potatoes, etc.; cup of coffee; green apple, etc.). The differences in Hg emission obviously relate directly to the density, texture and abrasiveness of the foods. Surely the CDAEP does not believe that the duration and intensity of chewing is the same for a bread roll and a green apple. The Richardson report did not misunderstand these papers.
15	15-24	"... in the paper by Sallsten et al. (1991) the authors are assuming..."	This paper is in Swedish and will not be translated. If bruxism can not be defined as "abrasive stress" then what is it? An argument based on semantics, as being offered in the CDAEP report lacks credibility and is not a sound technical or scientific rebuttal of the Richardson report. Note that they do not dispute the citation of Marek (1992) which deals with corrosion particles from amalgam.
15	25-35	"In dealing with the question of methylation..."	Richardson does not understand the point being made. The Richardson report concluded that their was no evidence to suggest that this was occurring. However, a recent study has measured methylmercury in the mouth in association with amalgam fillings, indicating that amalgam mercury is being methylated in the mouth by oral bacteria.
15 16	36-39 1-7	"The Richardson report states on page 17, ..."	In fact, the data can be interpreted either as done in the Richardson report or as presented by the CDAEP. Longer duration in the lungs permits more mercury to contact respiratory surfaces through simple diffusion. Richardson agrees that the key point here is that slower breathers appear to absorb more mercury. However, there were insufficient data to permit a quantitative treatment of the behaviour of slow breathing. Therefore the criticism is moot. This in no way illustrates a significant lack of attention to the interpretation of the research literature, as suggested by the CDAEP.

Page	Line	CDA Comment or Criticism	Response
16	8-22	"On page 71 of the Richardson report the paper by Rowland et al. (1994) ..."	Richardson doesn't understand the point that the CDAEP is trying to make. In section 7.2 (Teratology/reproductive toxicology) the Richardson report concludes that "There is no evidence to suggest that any disruption of fertility or reproduction will occur at levels of Hg exposure associated with amalgam fillings." With regard to the study by Rowland et al. (1994), the Richardson report correctly cites the results of that study ("Rowland et al. (1994) reported apparent increased fertility, relative to unexposed controls (no use of amalgam) in a subset of dental assistants with low Hg exposure..." and "fertility in a subset with higher Hg exposure... was reportedly reduced to 63% that of controls."). No error was made in the citation and the Richardson report never extrapolated these results to amalgam bearers beyond the fact that there was no evidence to suggest that this is an issue.
16	23-	"The lack of critical evaluation of the literature is pervasive..."	What critical comment does the CDAEP want? The studies cited were published in the peer reviewed literature and, therefore, can be considered credible. If the Richardson report was undertaken to quantify the overall reduction in fertility of the Canadian population with amalgam fillings, or to quantify the teratological consequences of in utero exposure to mercury from amalgam, then these citations and others would have been given greater attention. However, this was not the focus of the Richardson report. The literature review was undertaken to determine the most appropriate health outcome or effect(s) upon which to base a population-based risk assessment. The most appropriate endpoint is based predominantly on the size and quality of the database of toxicological studies and epidemiological studies available in the published literature. The effect of greatest concern was CNS impairment. That is where the effort was focused.
16 17	33-39 1-11	"It is surprising that this controversial paper by Drasch et al. (1994) was not critically reviewed in any detail in the Richardson report. ..."	Richardson believes that this paper is only controversial to the dental community (and the CDAEP). It very clearly reports strong correlations (Spearman rank) between maternal amalgam load (number of teeth with amalgam fillings) and levels of mercury in liver and kidney tissue of aborted fetuses. Work with animals by Mats Berlin of Sweden, Vimy and Lorscheider in Canada and others demonstrate that this is consistent with animal experiments involving mercury vapour exposure of pregnant animals during gestation. This is a very real concern and has recently been extensively reviewed by Mats Berlin for the Swedish government. Implied weaknesses in the Drasch et al. (1994) paper are unfounded.

Page	Line	CDA Comment or Criticism	Response
17	12-29	"The total mercury concentration were calculated as ..."	This paragraph in the CDAEP report demonstrates a significant lack of understanding of statistical analysis, both at the theoretical and practical levels. Certainly the data were non-parametric. Virtually all biological data are non-parametric, reflecting a log-normal rather than a normal distribution. There are two equally valid and statistically-appropriate approaches to employ for the analysis of non-parametric data: a)transformation of the data such that the data are normally distributed, or b) application of non-parametric tests. The methods applied by Drasch et al. to the analysis of their data were appropriate to the data presented. Contrary to the CDAEP implied position that the number of filled teeth is not a sufficient measure of amalgam load, it is likely that a stronger correlation would have been evident than that reported in the Drasch et al. paper if another more precise measure of amalgam load which incorporates size, shape and location of fillings had been used. Regarding the use of number of fillings rather than another measure of amalgam load, the statistical implications of this were discussed in the Richardson report (see Section 9.0 Discussion and Risk Characterization). Skare and Enqvist (1994) found that the same amount of data variation in mercury exposure was explained by either number of filled tooth surfaces, number of occlusal surfaces, or total amalgam surface area. Therefore, increased precision in source strength (amalgam load) does not increase the amount of variation in the dependent variable explained by the independent variable. This is probably due to the inter-individual variability (due to genetics, behavioural patterns, etc.) inherent in the human population which introduces variation in the uptake, metabolism, tissue distribution and excretion of mercury, as well as in individual susceptibility to effects.

Page	Line	CDA Comment or Criticism	Response
17 18	30-39 1-5	"It is important to note that we do not know the source of the mercury or the toxicological consequences, if any, of the mercury in the various tissues reported in this paper...."	The source of mercury in the fetal subjects of the Drasch et al. paper is quite obvious - the mother. The fetal tissue mercury levels correlate strongly with maternal amalgam load. It is incumbent upon any risk assessor or toxicologist to conclude that the source of the mercury is the source which correlates with the measured tissue levels. The CDAEP is now introducing the argument that no study can be believed. Richardson agrees that the toxicological consequences of this fetal exposure are unknown. In section 7.2 of the Richardson report it states "The overall implications of low level prenatal Hg exposure for neuropsychological development are unknown at this time." The CDAEP goes on to question the basis of restrictions on the use of amalgam implemented by the German Health Authorities. This comment is misplaced here becasue the Richardson report never discussed the German restrictions, never quantitatively evaluated fetal, neonate or infant mercury exposure, and never drew any conclusions regarding this exposure or what, if any, use restrictions might be appropriate in these age groups.

Page	Line	CDA Comment or Criticism	Response
18	8-11	"...the conclusions of this particular paper by Boyd et al. (1991) have been strongly criticized. ..."	The only criticism of the Boyd et al. paper that has ever been brought to Richardson's attention was verbal criticisms by a representative of the CDA and a paid consultant of a dental amalgam manufacturer both of whom disliked the study very much. However, it is an elegant animal study. Toxicological investigations are routinely conducted in animals because it is unethical to conduct such studies in humans. Note that the Malvin (1991) citation cited by the CDAEP is an unpublished, second hand quote. The analysis purported to demonstrate that the sheep in the Boyd et al. study had 'improved kidney function' is not available for critical public examination. The researcher to whom the second hand citation is credited (J.W.Osborne, 1992) is a dental materials researcher with no toxicological or risk assessment expertise whatsoever. Interestingly, Osborne has published a paper stating that amalgam use does present potential risks (Wolff, Osborne and Hanson, 1983). These authors state "It is possible that we have accepted a potentially dangerous material as being safe." Again, these comments stray from the purported purpose of the CDAEP report - to criticize the Richardson report. The paper by Boyd et al. was never cited in the Richardson report, nor was any weight placed on animal studies in the Richardson report.
18	12-14	"The data in the Drasch et al. (1994) paper cannot be used to claim that there is a causal relationship between the mercury present in the tissues of children and fetuses and the number of amalgam fillings in the mother."	In the case of fetal tissue mercury levels, certainly it can. The CDAEP should examine texts on applied statistics regarding the application and interpretation of correlation, regression and other statistical relationships.
18	15-16	"Furthermore the paper cannot be reliably used to calculate the body burden of mercury which is due to the presence of amalgam fillings."	The Richardson report never undertook such a calculation, so Richardson is uncertain as to the point of this comment with regard to the Richardson report.
18	16-29		The further emphasis and comment on the Drasch et al. paper is misplaced given the fact that it did not form the basis of the risk assessment undertaken in the Richardson report.

Page	Line	CDA Comment or Criticism	Response
18 19	30-38 1-2	"The process of simply quoting from published papers without critical analysis..."	In the Richardson report, critical analysis was focussed on the critical areas of the risk assessment - occupational studies relating to CNS impairment due to mercury exposure; data relating to the factors which contribute to exposure. The CDAEP has spent an incredible amount of time and energy criticizing papers that represent little or no part of the Richardson report. Richardson accepts that the CDAEP does not like his writing style. However, the journal in which the report is published considered the treatment of the data and information to be quite adequate. Obviously, Richardson should not have expected the Richardson report to be accepted for publication in a dental journal. This is why it was sent to a journal which specializes in risk assessment; so that it would get a fair and unbiased peer review during its consideration for publication.
19	3-15	"It is not possible to draw conclusions... The Richardson report fails to meet these criteria and does not provide a comprehensive basis for the thesis put forward."	Obviously, Health Canada disagreed or it would not have released the Richardson report, would not identify it as a departmental report, as it does, and the peer-reviewed science journal to which it was submitted would have rejected it, which it did not. The Richardson report is the single most exhaustive review and analysis of mercury exposure and risks from amalgam published by any organization. It is more detailed, exhaustive and quantitative than the exposure assessment (Appendix 3) in the CCEHRP report, or the WHO (1991) treatment of this issue.
19	30-36	"...one important aspect which has been completely ignored... is the question of alcohol consumption."	The Richardson report did not single out alcoholics as a specific at risk group. Research indicates that alcoholics have lower tissue levels (brain and other tissues) than non-alcoholics. However, alcoholism does not reduce exposure or absorption, it reduces or alters mercury vapour metabolism, tissue distribution and excretion. Therefore, alcoholics with amalgam fillings will have the same mercury exposure as non-alcoholics, but will have different pharmacokinetics. They may also have lower incidence of CNS effects, given that levels are lower in the brain. However, as mentioned, alcoholics were not selected as a specific at risk group.

Page	Line	CDA Comment or Criticism	Response
20	3-21	3.1.1 Epidemiological Dental Data	As mentioned previously, the Richardson report evaluated the representativeness of the data on numbers of filled teeth in the Canadian population. Comparison with more recent U.S. data and comparison of Canadian data for 13 year olds, the only age group for which more recent Canadian data had been published, indicated that the data were representative. An indirect analysis, presented in the Richardson report, suggested that the Richardson report may have underestimated the average number of amalgam fillings in adults by 30 to 50%. Today's adults have had more dental restorative work than their parents did. This would have increased the estimated exposures by 30 to 50%. However, this evidence was indirect so it was not incorporated into the analysis. Despite a request for more recent data to the CDA, they were unable to provide any Canadian data pertaining to the number of filled teeth in the Canadian population. Therefore, the data available from Health Canada was employed.
20	22-23	"...this data are reasonably representative of the current Canadian occurrence of filled teeth. However, this is not acceptable as a scientifically valid statement."	Despite the CDAEP's comments, the CDA could provide no data to support their allegation that the data were not representative. The Richardson report goes to great lengths to compare the available data to other available data sets (U.S., Canadian 13 year olds examined in mid 1980's) and found them, through statistical comparisons, to be comparable.
20	23-24	"It is not possible to extrapolate from this 25 year old epidemiological data to present day."	On the contrary, if all statistical indicators demonstrate the data are comparable, then the data can be applied. The most objective approach is to rely on objective statistics rather than on opinion.
20	24-27	"It is also clear,... assessment of body burden... renders the exercise conducted by Health Canada to be quite meaningless."	First, the CDAEP repeatedly confuses exposure with body burden. The Richardson report assessed exposure, not body burden. Secondly, far from being meaningless, the Richardson report is the only risk assessment of its kind and has contributed significantly worldwide to the conflicting reports and opinions which have been rendered on the issue of amalgam. The most objective approach to risk assessment is to establish a reference dose following standardized procedures, quantify exposure to the chemical of concern, and then compare the two.

Page	Line	CDA Comment or Criticism	Response
20	27-32	"What is worse... pure speculation."	Speculation was not involved. U.S. and Canadian populations are routinely equated in terms of standard of living, living conditions, health status, etc. Comparison of Canadian data to U.S. data is certainly acceptable and is not speculation. In the Richardson report, citations regarding the decline in filled teeth in children were presented as follows: "For Canadian school children, average DMFT score had declined in Ontario by about 50% between 1950 and 1984 for children aged 5 to 13 years (Johnston et al. 1986), in Alberta by 35% between 1978 and 1985 for children aged 13 years (Lizaire et al. 1987), in Quebec by 33% between 1977 and 1984 for children aged 13 and 14 years (Payette et al., 1988), and in B.C. by 44% between 1960 and 1980 for children aged 5 to 15 years (Hann et al. 1984)." For the increase in filled teeth in the adult population, U.S. statistics were offered, as follows: "The number of filled teeth in the adult North American population has increased since the early 1970s. For U.S. adults aged 18 years and older, the average number of filled teeth in 1985-86 was 9.05 (USDHHS 1987) compared to an average of 6.9 in 1971-74 (USDHHS 1993). This represents an increase of about 31% over the intervening decade." Therefore, the comments of the CDAEP are unfounded.
20	34-36	"...the best estimate ... is not good enough."	The 'best estimate' is always the best quantitation to apply to any variable in a risk assessment.
21	1-5	"... these goals cannot be achieved if we have no data on the dental status of the Canadian population on which to base the assessment."	As previously discussed, the Canadian data on numbers of filled teeth is representative and, therefore, the goals of the Richardson report were achieved, at least to the satisfaction of Health Canada and the journal in which it was published.

Page	Line	CDA Comment or Criticism	Response
21	7-8	"WHO... 1 ug Hg/m3 of air acceptable..."	Richardson can cite the ATSDR which considers only 0.014 ug Hg/m3 as acceptable (5 times lower than the Richardson TDI). It is readily apparent to anyone knowledgeable in this area that there is uncertainty in what constitutes a safe level of Hg vapour exposure. That being said, the Richardson report applies the procedures common to the Canadian regulatory system to derive a reference dose (TDI) for mercury vapour exposure. This is set independently of what was done by the ATSDR or by WHO.
21	11-13	The dose estimations proposed in section 5.0 ... safe dose derive in section 8.0 are inconsistent."	Without some further delineation of these 'inconsistencies', this criticism can not be addressed.
21	13-15	"There are no observations...it must therefore be assumed that this dose is safe."	This is a misleading statement. Their statement implies that observations have been made when, in fact, they haven't been. Certainly, background exposure to lead in young children was long thought to be 'safe' until researchers investigated IQ scores.
21	15-16	"The relationship between background dose and TDI is not addressed in the report."	A reference exposure level (TDI) is derived independently of information on the exposure (background or otherwise) of the critical population (in this case amalgam bearers). If background exposure is less than the TDI then, and only then, can the background exposure level be considered safe (free from known risk).
21	17-25 + figure 1	"The calculation in the Richardson report of the ..."	The TDI is based on a single key study (Fawer et al., 1983). This is how reference doses are derived. Richardson does not understand how the CDAEP generated Figure 1. The TDI is only a single value (0.014 ug/kg-day). Figure 1 presents the TDI as multiple values ranging from 0.00 to 0.04 (units unspecified in CDAEP's Figure 1). Therefore, Richardson has to conclude that the CDAEP does not understand the concept of reference dose (TDI) derivation.

Page	Line	CDA Comment or Criticism	Response
22	1-17	"The Fawer et al. (1983) paper was a last minute second choice..."	Richardson originally favoured a paper by Ngim et al. (1992) for derivation of the TDI. The Ngim study was on dentists (therefore mercury exposure related to amalgam use), had a good sample size (n=98), had representation of both men and women. Following peer review, Richardson agreed to comments offered by the primary author of the ATSDR Toxicological Profile on mercury (R. Canady) that the Fawer et al. study was superior in some other respects (researchers were blind to mercury exposure parameters prior to administering the tests of hand tremor) which made it somewhat preferable. This is what peer review is for, to evaluate your logic and provide advice.
22	21-25	"In the case of the Ngim et al. (1992) data an uncertainty factor of 10 for LOAEL and 5 for the inter-individual variation..."	The Ngim et al. study permitted a statistical analysis of inter-individual variation in neurobehavioral response to Hg vapour exposure. This direct analysis produced an uncertainty factor of 5 for inter-individual variability in toxic response. In fact, the same was true of the Echeverria et al. (1995) study which was used to derive a tolerable urine Hg concentration. The Fawer et al. study did not present data to permit a statistical analysis of the inter-individual variability in toxic response. Under such circumstances, standard practice dictates an uncertainty factor of 10 for this factor. Thus, a total uncertainty factor of 100 was applied to the Fawer et al. data. This is consistent with ATSDR and their treatment of the Fawer data, although they also apply a further adjustment of approximately 5 to account for the fact that Fawer et al. subjects were exposed for an average of 15.3 years whereas lifetime exposure is considered to be 70 years. (70/15.3=4.6)
22	29	"The original Draft TDI is 43% higher..."	The CDA had an opportunity to comment on the first draft report, through the peer reviewer which they were invited to appoint. Their comments on the first draft are out of place here. Their comments should be directed to the final Richardson report.
22	33-37	"...what is interesting..."	Revisions to the first draft included revisions to both the TDI and to estimates of exposure. Therefore, it is not surprising that the estimated number of fillings required to produce a dose equivalent to the TDI was 4 for adults in both the first and final drafts.

Page	Line	CDA Comment or Criticism	Response
23	11-13	"...most reviewers would presumably not then ..."	Considering that Richardson took the advice of the peer reviewers in the selection of the Fawer study, it would seem somewhat unnecessary to revisit this issue with them. Far from being a "poor second choice", the Fawer study was recommended by the peer reviewers and, therefore, obviously meets with their full approval. At one hand the CDAEP criticizes if peer review comments are not accepted and at the other hand criticizes when peer review comments are accepted. Some consistency would demonstrate objectivity and credibility in their comments.

Page	Line	CDA Comment or Criticism	Response
23	16-37		Papers by Scheckmann (1979) and Lob (1965) are irrelevant to the review of the Richardson report. They were neither relied upon nor cited. The quality of working conditions reported by Lob (1965) are irrelevant. Mercury exposure occurred in subjects of the Fawer et al. study. Mercury vapour is mercury vapour, regardless of the source. To 'argue' that workers exposed to mercury in the Lob study will have recovered by 1983 is both unfounded and uninformed. A variety of studies of occupational mercury exposure demonstrate that CNS impairment resulting from occupational exposures is irreversible (discussed in the Richardson report). Therefore, they would not likely have fully recovered. The emphasis placed on the Lob (1965) study is surprising as the CDAEP has criticized the Fawer study as being dated (old) and here the CDAEP emphasizes a paper which is 18 years older. An enormous weight of evidence now exists to demonstrate CNS impairment due to mercury vapour exposure, including at levels at or near levels of exposure experienced by persons with dental amalgam. This weight of evidence is discussed in the Richardson report and in Richardson (1998), Richardson and Allan (199**6**), by the U.S.EPA (IRIS, 1998), U.S.ATSDR (1994), Ratcliffe et al. (1996). To rely on 1965 data and information and to ignore the recent literature is unacceptable.
24	1-13		Richardson fails to understand the relevance of this discussion of working conditions to an evaluation of mercury toxicity and exposure from dental amalgam. Working conditions do influence exposure and it is to the credit of the industries involved that working conditions have improved. Past peak exposures may have some relevance to the effects observed in the Fawer et al. study. However, dental patients also experience peak, short term exposures when having amalgam fillings removed and replaced. These inhalation exposures, the result of exposure to mercury vapour and particulate amalgam (sub-micron amalgam particles are generated in large quantities due to drilling, grinding and polishing with high speed dental instruments (Richards and Warren, 1985; Nimmo et al. 1990)), would mimic similar short term peak exposures in workers and, therefore, this does not reduce the relevance of the Fawer et al. study to the establishment of a reference dose (TDI) for mercury vapour.

Page	Line	CDA Comment or Criticism	Response
24	14-24		No study is ever 'ideal'. To think that such a study exists is to fail to recognize the limitations of time, money, and other factors which influence study design and hypothesis formulation. However, when the weight of evidence for a particular effect is as substantial as it is for the CNS effects of mercury vapour, it can not be argued that the effect is not 'real' simply because one study is not 'ideal'. This is to argue that, since we can not prove conclusively with one ideal study whether the chicken or the egg came first, that we must conclude that both the chicken and egg do not exist.
24	19-24	"The Fawer et al. (1983) study can not be classified as a "Critical Study" - yielding a no observable adverse effect level (NOAEL) which can be used as the basis for a reference dose (RfD) for mercury from amalgam fillings in the Canadian population. ..."	Here, again, the CDAEP demonstrate a lack of understanding of risk assessment. The reference dose (TDI) is established for mercury, regardless of its source. Mercury vapour from amalgam will not differ toxicologically from mercury vapour from any other source. The differences relate to level of exposure, not toxicology. Second, the Fawer et al. study presents a LOAEL not a NOAEL. Finally, both the U.S.EPA and the U.S.ATSDR have also employed the Fawer et al. study to define a LOAEL from which a reference exposure level is derived. Obviously, the Fawer et al. study is a suitable study for such a purpose, despite the fact it is not 'ideal'.
24	25-26	"The statistical significance of the data ... is not very strong."	Again, the CDAEP demonstrate a lack of knowledge and understanding of risk assessment. Besides statistical significance, a risk assessor must examine the weight of evidence offered by other similar studies. Also, a risk assessor must examine the 'biological' significance of these studies. It is not uncommon to interpret a trend or relationship as biologically significant even when there is not statistical significance. The CDAEP's statistical opinions aside, the weight of evidence for CNS impairment due to mercury vapour exposure at levels near to, or in the range of, exposures received by persons with amalgam is such that it can not be ignored.
24	26-33	"Anger and Sizemore (1993)..."	What the CDAEP does not recognize or discuss is that as the degree of difference between the exposed and control populations increases, the sample size required to detect those differences is decreased. Obviously, the Fawer et al. study, and numerous other studies of the CNS effects of low level mercury vapour exposure, are more significant or the differences between exposed and control groups were greater than assumed by Anger and Sizemore in their theoretical discussion of sample size requirements.

Page	Line	CDA Comment or Criticism	Response
25	bullet 1		No epidemiological study ever sets out as its main purpose or hypothesis to derive a NOAEL or LOAEL. The null hypothesis would be defined such as: H_0: mercury vapour exposure has no effect on hand tremor. The study would then be designed in a manner to attempt to prove the null hypothesis false. This is 'the' basic scientific method.
25	bullet 2		It is true that dose-response data were not reported in the Fawer study. However, the weight of evidence offered by numerous other studies makes this a minor, perhaps moot, point. This was certainly the opinion of the U.S.EPA (IRIS, 1998) and ATSDR (1994).
25	bullet 3		The Fawer et al. study was recommended by of ATSDR during peer review because they had obtained additional information that the study had been conducted in a blind fashion. This was the major strength of the Fawer study compared to the Ngim et al. study which was known not to have been conducted blindly. This was the main reason that peer review advice was accepted and the Fawer study employed to derive the TDI.
25	bullet 4		Richardson fails to see the relevance of this statement. A measurement was defined which demonstrated a significant difference between the exposed and control groups. Specificity in the neurological effects of mercury is not uncommon, being repeatedly reported and discussed in numerous other papers on the CNS impact of occupational mercury exposure.
25	bullet 5		This point is greatly outweighed by the weight of evidence for CNS effects of mercury vapour exposure. If this study and the impact it reports were an aberrant result, then all other studies of this and other CNS impairments would be negative. However, this is not the case, as reviewed in the Richardson report and by Richardson (1998), U.S.EPA (IRIS, 1998), Ratcliffe et al. (1996), ATSDR (1994) and WHO (1991).
25	bullet 6		As previously mentioned, persons with amalgam also suffer peak exposures during dental procedures. Given this fact and the weight of evidence demonstrating CNS impairment, this comment is not relevant to the issue.
26	bullet 1		This criticism is moot given the weight of evidence demonstrating that the effect reported in the Fawer et al. paper is not spurious or aborant.

Page	Line	CDA Comment or Criticism	Response
26	bullet 2		As did the U.S.EPA and the ATSDR, the Richardson report adopted the mean air mercury concentration as the LOAEL of the Fawer et al. study. The true LOAEL and NOAEL are obviously lower than this mean value.
26	bullet 3		This is categorically false. It is better to use human epidemiological studies to set reference doses for people than to use animal studies. Such human studies are routinely used to quantify the toxicological consequences of chemical exposure. Other examples include benzene, asbestos and other industrial chemicals where impacts have been observed in occupationally-exposed individuals (primarily healthy men) and these data are employed to establish regulatory reference exposure levels for the general population.
26	bullet 4		This has been commented upon previously.
27	bullet 1		These arguments do little to alter the fact that the Fawer et al. paper was the best study from which to establish the TDI for the Richardson report, for the ATSDR and for the U.S.EPA.
27	bullet 2		As previously discussed, the Fawer paper was appropriate at the time. Richardson will concede that papers released since 1995, including one by Echeverria et al. due out imminently, may prove to be a more suitable basis for a revised reference dose or TDI. The recent evidence suggests that the TDI should be lower.
27	bullet 3		Various studies have found exposure level, exposure duration or a combination of the two to be the best predictors (regressors) of CNS effects. Given the long duration of placement of amalgam in a dental patient, this does not preclude the application of the Fawer et al. study to the derivation of a TDI to be applied to mercury vapour exposure from amalgam.
27	bullet 4		A measurement was defined which demonstrated a significant difference between the exposed and control groups. Specificity in the neurological effects of mercury is not uncommon, being repeatedly reported and discussed in numerous other papers on the CNS impact of occupational mercury exposure. If the CDAEP understood statistics they would understand that a paired t-test is designed specifically to compare data that are not independent (i.e., from the same individual).

Page	Line	CDA Comment or Criticism	Response
28	bullet 1		This is false. First, the measurement of hand tremor was done under clinical conditions with equipment specifically designed for the purpose. Most risk assessors would consider this to be a clinical measurement and a clinical effect. The term pre- or sub-clinical as used in the Richardson report related to the fact that the impairment did not result in a defined disease state such that hospitalization or other medical treatment was necessary. Regardless, numerous examples exist, the most notable being lead, where 'sub-clinical' effects are used as a basis for risk assessment. In the case of lead, an individual child can not be diagnosed with lead exposure and IQ impairment on the basis of his/her IQ score alone. In this sense, impairment due to lead exposure can not be 'diagnosed' in a doctor's office. The effect can only be observed by comparing the IQ scores of groups of lead exposed and un-exposed children, in which case a slight shift to lower average IQ score has been observed. This in no way reduces the significance of lead exposure. The same is true for low level mercury exposure where an individual can not be diagnosed as impaired on the basis of individual tests of tremor, cognitive function, etc. Rather, the results of a group of exposed individuals must be compared to those of a control group. In this sense, then, the effects of mercury are 'sub-clinical'.
28	bullet 2		The CDAEP offers no proof of any error in units for blood mercury levels in the Fawer et al. paper. No error has been reported elsewhere such as by the ATSDR, the U.S.EPA, or the WHO, all of which cite this study.
28	bullet 3		The hand tremor reported by Fawer et al. was associated by the authors themselves to the average air concentration reported by Fawer et al. No correlation was reported and none was required as the average air level for the exposed group was employed as a LOAEL.
28	bullet 4		As noted in previous comments, the CDAEP does not like the Fawer et al. paper.

Page	Line	CDA Comment or Criticism	Response
29	2-3	"The scientific literature does not contain any study which links mercury from dental amalgam fillings and an observable adverse clinical effect."	This is not quite true. Articles by Godfrey (1990) and others have reported that clinical symptoms were alleviated when amalgam was removed. However, there are no epidemiological studies investigating appropriate (CNS) effects in a group of persons with amalgam to a control group with no (and never having had) amalgam fillings. This is acknowledged at the outset of the Richardson report and is precisely why the methods used were applied.
29	16-18	"It is interesting to note that some 60% of the 74 data points shown in figure 5.19 (page 43) fall outside the 99% confidence limits of the regression line"	This again demonstrates the CDAEP's lack of understanding of basic statistics. The 99% confidence limits relate to the regression line, not the data points. The purpose of the confidence limits in this case are to demonstrate the potential variation in the regression line. **The interpretation is that there is a 99% probability that the true regression line lies within the confidence limits. In fact, as the number of data points increases for defining the regression line, the confidence limits become narrower and the number of points lying outside those confidence limits will increase, not decrease.** Further, the CDAEP implies that the data points should fall neatly on the regression line, but this is to completely misunderstand the nature of biological data. Genetic variation, behavioural variation, etc. introduce scatter in biological data. A simple course in biostatistics would make this clear.
29	18	"the graph does not have an 'r' or a 'p' value."	Values for r (regression coefficient) and p (statistical significance) were given by Skerfving (1991) and did not require repeating.
29	23-25	"...deducted from all of the other data points, thus giving... recalculation... r=0.453..."	Again the CDAEP demonstrates a lack of understanding of basic statistics. First, you would not deduct the values for zero fillings from the other raw data in this form of analysis. What would be done would be to retain the slope of the graph, but to adjust the final exposure estimates to account for the 'background' urine mercury Hg level such that only Hg in urine arising from amalgam was considered in the calculations of dose from amalgam. And, in fact, this is precisely what was done in the Richardson report. Admittedly, this is more clearly and explicitly described in the published manuscript (see equations on page 741 of Richardson and Allan, 1996).

Page	Line	CDA Comment or Criticism	Response
29 30	28-38 1-8	"...in order to make use of the mercury in air values... it was necessary to find a conversion...redefining the regression model of Roels et al. (1987) specifying a Y intercept equal to 0.45 ug hg/g creatinine in urine..."	By redefining the Roels et al. regression with a Y intercept of 0.45, the revised regression fit the data statistically equally well as the original analysis by Roels. The data fit is presented graphically in Figure 5.20 of the Richardson report. The Roels et al. paper only examined persons with occupational exposure in the range of about 10 to 100 ug Hg/m3 and urine Hg levels between about 10 and 100 ug/g creatinine. It is completely logical to expect those workers with no amalgam and no workroom exposure to mercury vapour to have a urine mercury level similar to others with no amalgam and no occupational exposure, such as those in the Skerfving data with no amalgam. The data were not "forced". The data fit is too good to suggest that the data were forced.
30	9-20	"In the Richardson report...Fawer et al...."	Fawer et al has absolutely nothing to do with the analysis of exposure. Besides, the air levels in the Fawer study, not the urine levels, were used to derive the TDI.
30	21-39	"A further inconsistency..."	As mentioned, the Fawer et al. study had nothing to do with estimation of exposures from amalgam. The CDAEP citation of Echeverria et al. (1994) should be 1995. The fact that the controls in the Echeverria study had undetectable urine mercury levels despite removal and placement of amalgam likely reflects excellent office mercury hygiene practices of the dentists involved. It certainly reflects much lower exposure.
30	38-39	"It is clear that conversion from mercury in air to mercury in urine is not a simple process."	Certainly it was not simple, but it is intuitively and computationally correct. Interestingly, other authors took the exact same approach at about the same time the Richardson report was being formulated (Weiner and Nylander, 1995). This independent development of the same approach, and its peer reviewed publication in yet another journal, demonstrates that this approach is scientifically valid.
30 31	39 1-2	"Yet in spite of this the Richardson report made use of this as a very necessary key step in order to produce the TDI."	This is incorrect. The mathematics being discussed relate to determining exposure and had absolutely nothing to do with the TDI. The TDI was derived following standard procedures previously discussed. The estimation of exposure had nothing to do with the derivation of the TDI.

Page	Line	CDA Comment or Criticism	Response
31	3-12	"Further calculations can be made..."	First, based on the regression equation published by Roels et al., an air concentration of 26 ug Hg/m3 predicts a urine Hg concentration of 36.46 ug/g creatinine, not the 31.72 claimed by the CDAEP. This calculation is simple. Second, the regression redefined by Richardson predicts a urine Hg concentration of 31.91 ug/g creatinine for an air concentration of 26 ug/m3. The difference between these is 14.2% ((36.46-31.91) ÷ 31.91 X 100) , not 36% as claimed by the CDAEP. Obviously, there apprears to be a lack of understanding of the publications they are citing and the basic mathematics they are attempting to compute.
31	13-27	"Using the relationships...."	Where did an analysis of blood Hg levels come from? The Richardson report focused on urinary levels. No attempt was ever made to employ Hg levels in blood.
31	27-29	"... it would seem unwise ... using... the data reported in the Fawer et al. (1983) paper."	The CDAEP does not understand the Richardson analysis. Fawer was not used in the analysis of exposure nor in the conversion from air to urine mercury levels.
31	29-33	"In spite of these obvious problems..."	The 'obvious' problems would appear to arise from the failure of the CDAEP to be able to differentiate between the steps and procedures used in the Richardson report to derive the TDI and to estimate exposure. As previously mentioned, the 'conversion' employed by Richardson was independently developed and published by Swedish researchers, thus confirming its scientific validity.
31 32	34-38 1-11	"The Richardson report ... the Agency for Toxic Substances and Disease Registry (ATSDR) (1994) does not claim..."	The primary author of the ATSDR 1994 Toxicological Profile on Mercury was a selected peer reviewer for the Richardson report. His advice, in peer review comments and subsequent communications, was to use the Fawer study specifically because, at that time, it was the most methodologically sound study. Why else would the ATSDR select the Fawer study for derivation of their minimum risk level? They did not go out of their way to select the worst study. Certainly the Fawer study had weaknesses, as all individual studies do (as previously discussed). Based on comments from ATSDR, the CDAEP is incorrect. The ATSDR publication can be used to support the selection of the Fawer study.

Page	Line	CDA Comment or Criticism	Response
32	12-27	"The question of peak exposure effects are well documented...."	As previously discussed, people with dental amalgam receive peak exposures during the removal and replacement of these fillings. They also have exposures of long duration, starting when amalgam fillings are first placed in their teeth. Therefore, this does not preclude the use of the Fawer study to set the TDI. The weight of evidence, the numerous studies which demonstrate CNS impairment at levels of exposure near or overlapping with the levels experienced by persons with amalgam, can not be ignored.
32	29-38	"A study by Kishi et al. (1994) ... exposure related to neurological dysfunction is often reversible..."	The CDAEP agrees that studies repeatedly demonstrate that many of the CNS effects of mercury exposure do persist despite cessation of exposure. Given that the duration of exposure in persons with amalgam will approach or exceed 50 years, differentiating effects due to past or current exposure may be moot.
33	1-13	"The Fawer study...: The hand tremor test was not one of twelve tests selected ... by the Agency for Toxic Substances and Disease Registry in December 1992."	The CDAEP is fixated on the Fawer study. In 1983, the date of the Fawer study, and even in studies published in 1996, hand or extremity tremor was a standard procedure for investigating the neurological impacts of occupational mercury exposure. The fact that additional or alternate test batteries are being considered demonstrates a desire or requirement for improved methods in the occupational health field. Despite the statement made, the ATSDR still selected the Fawer study for derivation of their MRL for mercury vapour exposure.
33	14-31	"A recent study by Akesson..."	The Fawer study did not involve dentists. Other studies of dentists have demonstrated improved performance of manual dexterity tests, likely due to their constant use of their hands and subsequent practice of fine motor skills. It is not immediately clear how this applies to the Fawer study. If the Fawer study was the only study to report hand tremor or CNS effects due to mercury exposure, then Richardson might agree with the CDAEP on this point. However, their are numerous studies which demonstrate CNS impairment. A few of these studies are (in no particular order): Shapiro *et al.*, 1982; Langworth *et al.*, 1992; Ritchie *et al.*, 1995; Roels *et al.*, 1989; Echeverria et al., 1998; Echeverria *et al.*, 1995; Boogaard *et al.*, 1996; Cavalleri *et al.*, 1995; Gunther *et al.*, 1996; Singer et al, 1987; Roels *et al.*, 1982; Piikivi and Tolonen, 1989; Roels *et al.*, 1985; Verberk *et al.*, 1986; Uzzell and Oler, 1986; Levine *et al.;* 1982; Gonzalez-Ramirez *et al.;* 1995; Ngim et al. 1992; Liang et al., 1993; Piikivi and Hanninen, 1989

Page	Line	CDA Comment or Criticism	Response
33 34	32-39 1-15	“A major concern ... the ATSDR has listed 275 substances...”	Does the CDAEP mean to imply that, since there are so many chemicals in the environment that we can not determine which is causing harm and, therefore, no chemical exposure should be investigated, controlled or regulated?

Page	Line	CDA Comment or Criticism	Response
34	17-22	"Mason and Calder (1994)... the variability of urinary mercury measurements..."	As previously mentioned, all biological data are variable. It is difficult to draw conclusions from urinary measurements for individuals. However, conclusions regarding population-based predictions can readily be made.
34	22-26	"Higher concentrations of mercury have been found in morning samples..."	This is not true. An extensive evaluation of urinary mercury levels measured at different times of the day (Cianciola et al., 1997) has demonstrated that mercury levels in spot samples collected at different times of the day, and/or 24 hour urine collections, are virtually identical in Hg concentration, thus eliminating the timing of sample collection as an issue.
34	26-36	"Correction for creatinine... reduce the uncertainty..."	The Richardson report did use creatinine-corrected urine Hg concentration data for determination of exposure (doses) received by persons with amalgam. This, combined with the study of Cianciola et al., (1997) on the consistency of Hg concentration throughout the day eliminates concerns expressed by the CDAEP regarding uncertainty in these data.
34 35	37-38 1-9	"A study by Berglund and Molin (1996)..."	The CDAEP acknowledges the limited number of subjects in the Berglund and Molin study. Numerous other studies, conveniently omitted by the CDAEP, demonstrate a strong statistically significant, positive association between measures of amalgam load and urinary Hg concentration. These include: Skerfving, 1991; Aronsson et al., 1989; Akesson et al., 1991; Langworth et al., 1991; Jokstad et al., 1992; Svensson et al., 1992; Suzuki et al., 1993; Herrmann and Schweinsberg, 1993; Skare and Enqvist, 1994. Therefore, the Berglund and Molin study is the exception, not the rule. This association is consistent through numerous studies and can not be dismissed.

Page	Line	CDA Comment or Criticism	Response
35	10-30	"Many reports relating urine mercury concentrations to the onset of effects...have been reviewed by the WHO (1991); not all studies were able to detect effects."	The point being made by the CDAEP based on one or two citations is false, irrelevant, and misleading. Conflicting data always exist in the literature. One task faced by risk assessment is to resolve these apparent conflicts. The primary approach to this problem is to examine the 'weight of evidence' for or against the occurrence of effects due to exposure. The existence of one positive (detrimental) study and many negative studies indicates a weight of evidence against a problem. However, the existence of many positive (detrimental) studies and a few negative studies indicates a weight of evidence demonstrating a problem. The weight of evidence is overwhelming that Hg vapour exposure results in CNS impairment. This weight of evidence is briefly mentioned in previous comments, and is reviewed extensively in the Richardson report, by ATSDR (1994), by the WHO (1991), by the U.S.EPA (IRIS, 1998), by Ratcliffe et al. (1996), among others. It should be noted that the focus of the WHO (1991) review was on kidney effects. It was acknowledged in the Richardson report that the apparent threshold for clinical impacts on the kidney (with respect to the common occupational marker of proteinurea) is between 25 to 50 ug Hg/g creatinine in urine. Therefore, the Richardson report did not concern itself with effects on the kidney. It should also be noted that numerous recent studies, reviewed for the Swedish government by Richardson (Richardson, 1998), demonstrate a dose-dependent association between urinary markers of sub-clinical damage (cytotoxicity) of the proximal tubule and urinary Hg levels, beyond the more common measurement of clinical proteinurea. These include: Roels *et al.*, 1982; Roels *et al.*, 1985; Woods *et al.*, 1993; Langworth *et al.*, 1992b; Langworth *et al.*, 1997; Boogaard *et al.*, 1996; Piikivi and Ruokonen, 1989; Eti *et al.*, 1995; Baaregard *et al.*, 1988; Nuyts *et al.*, 1992; Cardenas *et al.*, 1993

Page	Line	CDA Comment or Criticism	Response
35 36	31-39 1-2	The data of Echeverria et al. (1995)... study does not measure the organic mercury..	Sample size takes on less significance with the overwhelming weight of evidence indicating the CNS impairment caused by Hg vapour exposure. MethylHg (organic) does not primarily appear in urine. Excretion in faeces is the primary excretion route, for about 90% of ingested MeHg dose (WHO, 1990). At low vapour exposure levels, urinary excretion represents on the order of 60% of Hg vapour excretion (ATSDR, 1994). As mentioned above, Cianciola et al. (1997) have extensively evaluated the influence of timing of urine collection on Hg levels and have found that it makes no difference to Hg concentration measurements. Therefore, the comments of the CDAEP were not effectively researched and are unfounded.
36	3-7	"There are several studies..."	Cianciola et al (1997) have examined Hg concentration data with and without creatinine correction and have found them virtually the same. Therefore, creatinine correction will have little impact on the trends observed between effects, amalgam load, and other variables with urinary Hg levels, whether or not creatinine correction is undertaken. This amounts to a data reporting preference amongst researchers, not one distinguishing valid from invalid data.
36	8-15	"However, the limitations..."	Virtually all authors acknowledge the limitations of their studies. If the study is the only one suggesting the effects or trends reported, then the limitations take on greater weight. However, as repeatedly pointed out, the weight of evidence is too overwhelming to suggest that the results are spurious, incorrect or that they can be ignored.
36	15-19	“In fact, table 2 of the Echeverria et al. (1995) study...”	It has been previously mentioned that the control group included in the Echeverria study demonstrates the success of good professional mercury hygiene practices in the dental office for reducing or eliminating mercury exposure in dental personnel.

Page	Line	CDA Comment or Criticism	Response
36	24-	"This study is totally unsuitable for establishing a LOAEL for risk assessment..."	This is incorrect. In fact, in an extensive review and evaluation of published studies on the neurological impacts of mercury vapour exposure, Ratcliffe et al. (1996) identified the study by Echeverria et al. as one of the best studies, which meet all of their critical criteria, for use to assess the hazards posed by mercury vapour. The value of the Echeverria et al. study is enhanced by the fact that it is the only occupational study where the control group was confirmed as having mercury exposure (measured as urinary mercury level) equivalent to members of the general public with no amalgam, not just exposure less than the exposed group. The urinary mercury levels of the control group were <0.5 ug Hg/L urine.
36	27-28	"...mercury exposures that are not comparable to that from dental amalgam fillings."	Mercury is mercury, regardless of the source. The mercury originating from amalgam will cause the same effects as any other source, when the level of exposure is the same. As no threshold has been determined for the CNS impairment resulting from mercury level exposure, the Echeverria study is appropriate for use to derive the tolerable urine concentration.
36	29-31	"A larger and much more comprehensive study on appropriate subjects..."	Richardson completely agrees. Given that the overwhelming majority of available occupational studies (i.e., the weight of evidence) indicates CNS impairment with mercury exposure, at levels close to and overlapping the level of exposure experienced by persons with dental amalgam fillings, Richardson agrees with the CDAEP that a major study is necessary to define the threshold, if one exists, and to quantify the proportion of amalgam-bearers that are suffering some degree of excess CNS impairment (compared to amalgam-free controls). However, the lack of that study, which the CDA has never initiated, does not invalidate the risk assessment presented in the Richardson report. If anything, the Richardson report adds weight to the immediate requirement for such a major study.

Page	Line	CDA Comment or Criticism	Response
36	31-39	"It is also unacceptable to base a LOAEL on the mean value of 36 ug/L when it is not known that this level would actually be sufficient to produce measurable differences compared with the control group. ..."	These two comments are unfounded. First, a mean value is routinely interpreted as a LOAEL. The most obvious examples come from the U.S.EPA and the ATSDR which both employed the mean exposure level in the Fawer study to define a LOAEL to establish their reference Hg vapour exposure levels. Secondly, the Echeverria et al. study did measure significant impairment due to Hg vapour exposure. Due to confounders such as alcohol consumption, which the CDAEP has insisted be taken into account, a direct comparison of average performance between exposed and control groups was not appropriate. Instead, a multi-factorial regression method, controlled for known confounders, was applied to their data. These analyses demonstrated a variety of positive associations between Hg levels in urine and measures of: integrated sum scores of a battery of cognitive and motor tests, verbal skill, various symptoms, mood.
36 37	38-39 1-2	In this regard, another study (Albers et al., 1988)..."	The (repeated) issue of peak exposures has been discussed above. Dental patients also experience peak exposures during removal and placement of amalgam fillings. Various studies demonstrate positive association of mercury exposure level, duration of exposure and/or peak exposures with CNS impairment. This should illicit a concerted effort to investigate how these influence CNS performance in persons with amalgam, not a concerted effort to deny any effect at all.
37	10-14	"Interestingly, Diana Echeverria publicly stated ..."	Richardson personally attended the conference in Arkansas and can not recall such a statement from Diana Echeverria. Regardless, Diana Echeverria was an invited peer reviewer of the Richardson report. Her comments to Health Canada do not indicate nor suggest any inappropriate treatment of her data. In fact, she submitted additional unpublished documentation to strengthen the section on the TUC. It should be noted that her peer review comments were in the possession of the CDA. It is interesting to note that they fail to mention it in the CDAEP review of the Richardson report.

Page	Line	CDA Comment or Criticism	Response
37	15-39	"Among all the parameters..."	The CDAEP has attempted to introduce any argument, no matter how hypothetical or speculative, to suggest that the Echeverria et al. study is somehow invalid or can not be used for risk assessment. Their comments are totally unfounded and without merit. Interestingly, Diana Echeverria has furthered her research on this issue, now having completed the evaluation of CNS impairment of dentists who's urinary mercury levels span 5 to 20 ug Hg/L, the lower range of which encompasses exposures arising from dental amalgam. Her latest study was presented in Sweden as part of that country's current re-evaluation of the amalgam issue. Her work is published, along with Richardson's, in the Swedish report which is publicly available. Also, her latest research is in press with a peer-reviewed journal and due for imminent publication.
37 38	39 1-8	"In the Echeverria et al. (1995) study, the mercury exposed and non-exposed groups showed no significant difference in the cognitive and motor function tests. ..."	As previously mentioned, the Echeverria et al. study did measure significant impairment due to Hg vapour exposure. Due to confounders such as alcohol consumption, which the CDAEP has insisted be taken into account, a direct comparison of simple average performance between exposed and control groups was not appropriate. Instead, a multi-factorial regression method, controlled for known confounders, was applied to their data. These analyses demonstrated a variety of positive associations between Hg levels in urine and measures of: integrated sum scores of a battery of cognitive and motor tests, verbal skill, various symptoms, mood. The CDAEP previously (in criticisms of the Fawer et al. (1983) study) emphasized the need for a battery of tests, such as that proposed by the ATSDR. Here, the CDAEP criticizes the Echeverria et al. (1995) paper despite the fact that it includes a battery of tests, involving many of those suggested by both WHO and ATSDR. Some consistency would increase the validity and credibility of comments.

Page	Line	CDA Comment or Criticism	Response
38	9-17	"The toxic effects of methyl mercury..."	What has methyl mercury got to do with the Richardson report? Again, it is apparent that the CDAEP will introduce any argument no matter how irrelevant to attempt to discredit the available research that indicates the potential hazards associated with mercury vapour exposure. As an interesting aside, both Health Canada and the U.S.EPA have both recently reduced their reference doses for methyl mercury. Despite the fact that people eat fish, and that many members of the Canadian (and U.S.) population exceeded the old reference doses, and now a greater proportion of the population exceeds the new reference dose, the reference doses were still lowered. Therefore, it should be obvious that the existence of exposure exceeding a reference dose does not make that reference dose invalid. Also, at no time have these two regulatory agencies suggested that just because exposure to methyl mercury is at a certain level that it must be safe. However, the CDAEP seems to think that this poor logic should be applied to the issue of mercury exposure from dental amalgam. This is further evidence of the lack of experience or expertise in regulatory risk assessment on the CDAEP.
38	18-25	"Urine mercury levels of 5 ug/L urine have been reported in dentists..."	People with amalgam experience exposures up to about 10 ug/L, which is not 2-3 ug/L below that of dentists, but can be equivalent or higher, depending on the number of amalgam fillings and other individual factors such as metabolism, excretion, etc. Richardson agrees that the average levels reported for chloralkali workers are about 50 ug/L (10 times greater than 5 ug/L). Virtually all of the occupational studies demonstrate CNS effects at this level. Surely, the CDAEP does not propose that this level would be safe in amalgam-bearing subjects? In fact, the published studies can not define the threshold, which is below 25 ug/L. Based on current methods for defining reference exposure levels, it must be predicted that the threshold is 50 to 100 times lower than 50 ug/L. The Richardson report, using methods employed in Canada, predicted the threshold to be 50 times lower than 36 ug/L, the average urine Hg level reported by Echeverria et al.
38	27-34	"The use of ..."	This has already been discussed.

Page	Line	CDA Comment or Criticism	Response
38	34-35	"However, the figure shows that the graph represents only the number of fillings between 10 and 25, thus 5 fillings are outside the range of the graph."	This is categorically false. If the CDAEP bothered to look at the study by Skerfving (1991) they would see that the range of number of fillings spans from 0 fillings to 25 fillings. No extrapolation was done.
38 39	36-38 1-3	"The tolerable urine concentration ... however, the unexposed control workers in the Fawer et al. study..."	The Fawer study has absolutely nothing to do with the CDAEP's current argument. What is the significance of the Fawer control group urine levels to the determination of a tolerable urine concentration based on the Echeverria et al. study? As previously mentioned, it is obvious that the Fawer control group was not free of Hg exposure, just that it has much lower exposure than the exposed group. Also previously mentioned is the fact that the Echeverria study is the only study in which the control group had exposure resulting in less than 0.5 ug Hg/L. As determined by Ratcliffe et al. (1996) Echeverria et al. (1995) is one of only few studies which meet all criteria making it ideal for risk assessment purposes.
39	3-14	"For example, Berglund (1990)... The above data clearly shows that a value of 0.7 ug/L as suggested in the Richardson report is very unrealistic"	The Berglund study supports Richardson's position, as does the Skerfving (1991) study, and others that amalgam free subjects generally have urinary mercury levels of <0.5 ug/L or <0.5 ug/g creatinine. These units are virtually equivalent(Cianciola et al., 1997). The amalgam-free subjects with 28.2 ug/L exceed the level of mercury in urine found in many occupationally-exposed individuals. Therefore, they are obviously not exposure free. No effort was made to resolve the source of this exposure. Such an obvious outlier must be resolved before it is assumed to be normal.
39 40	16-38 1-4	Section 3.3.4 Blood Mercury and the Number of Amalgam Fillings	Blood Hg levels were never discussed in the Richardson report so the relevance of this material is minimal. The CDAEP claims to present a correlation with the Fawer data. However, the raw data were not presented in the Fawer report and, therefore, this analysis is simply (and totally) fictitious.
40	5-25	"It has been suggested that mercury vapour may be transformed into highly toxic organomercury ..."	This point is not relevant. The Richardson report concluded that there were no data to support the contention that the conversion of Hg vapour to methylmercury was occurring and was, therefore, not pursued or discussed in the Richardson report.

Page	Line	CDA Comment or Criticism	Response
40	26-33	The proposed TDI in the Richardson report..."	Blood is the wrong medium to attempt what the CDAEP is proposing here. Only a small proportion of methylmercury ingested with fish is excreted in the urine. The majority (90%) is excreted in the faeces (WHO, 1990). Hg vapour, on the other hand, is excreted to a large extent in the urine; about 60% of total excretion at low levels of exposure (ATSDR, 1994). The rest is excreted in the faeces. However, both Hg vapour and methylmercury enter the blood stream. Therefore, blood is the bodily fluid most likely to contain mercury from both fish and vapour sources, thereby greatly confounding the measurement of mercury in blood in amalgam-free individuals. This potential confounding will be negligible in urine.
40	35-39	"According to professor Halbach..."	Professor Halbach's comments aside, the CDAEP should be citing the procedures for regulatory risk assessment developed and published by Health Canada.
41	1	"...low clinical relevance of the effect and its reversibility."	The CDAEP appears to suggest that CNS impairment in the form of either extremity tremor or cognitive function impairment is of low clinical relevance. Richardson disagrees. CNS impairment is relevant. The CDAEP suggests that the CNS effect is reversible. Several studies demonstrate that CNS impairment has proven irreversible despite years since exposure (Ellingsen et al., 1993; Andersen et al., 1993, Kishi et al., 1993, for examples).
41	3-8	"...necessary to evaluate more than one report, if available, with regard to the appearance of the effects in low-level range..."	The CDAEP obviously agrees that reviewing the weight of evidence is of paramount importance in determining if an effect is 'real'. So why did they not review that weight of evidence? The CDAEP has completely ignored the multitude of studies demonstrating CNS impairment due to Hg vapour exposure during their entire critique of the Richardson report. Richardson totally agrees that the weight of evidence is very important. This is why it was reviewed in the Richardson report, why it was reviewed by U.S.EPA, why it was reviewed by ATSDR, all of which concluded that no threshold for CNS impairment by mercury vapour has been defined, and that 26 ug Hg/m^3 represents a LOAEL, not a NOAEL. The CDAEP should have reviewed the full weight of evidence and offered 'valid' evidence of its non-existence before attempting what is a piecemeal, incomplete and biassed evaluation which only cites a few negative studies supportive of their assertion that Hg vapour exposure is not harmful, but ignores all of the positive studies that have been published.

Page	Line	CDA Comment or Criticism	Response
41	9-34	"The uncertainty factor..."	All the references and comments aside, the CDAEP must defer to the methods of Health Canada. At no time have they mentioned the methods or procedures of the agency for which the Richardson report was prepared.
41 42	35-38 1-5	"In a paper from 1991 by Magos..."	The Magos paper assumed that nephrotoxicity was the critical effect. However, the Richardson report, and all other serious treatments of low level mercury vapour exposure (U.S.EPA, ATSDR) acknowledge CNS impairment as the critical effect. Therefore, the Magos paper is irrelevant as it addresses the wrong endpoint.
42	6-12	"In Table 1 of the Fawer et al. (1983) paper, ..."	Richardson knows of no instance when an uncertainty factor was derived in the manner proposed by the CDAEP. It is unfounded and without merit. The CDAEP assumes that the Fawer control group was free of effects. This can not be concluded. First, it can only be assumed, in fact it is demonstrated, that the control group in the Fawer study had a lower incidence of hand tremor compared to the exposed group. However, there was no group in that study with urine Hg levels <0.5 ug/L, the level generally present in amalgam-free individuals. Therefore, the incidence of hand tremor in a true control group, one with urine Hg levels <0.5 ug/L, is not available. No data have yet been published reporting the range and 95% confidence limits of hand tremor in persons with urine Hg levels of <0.5 ug/L.
42	13-18	"...This is obviously inappropriate..."	The average exposure of the Fawer study is a LOAEL as detailed repeatedly above. The CDAEP does not understand the concepts, principles or practices of risk assessment.

Page	Line	CDA Comment or Criticism	Response
42	18-28	"The report also applied the maximum factor of 10 for inter-individual variation/sensitivity. This is also of doubtful validity..."	Only just on the previous page (page 41) of the CDAEP report, they cited Thomas Clarkson as an authority on uncertainty factors. They quoted: "human studies - a safety factor of 10 because threshold levels should not vary with more than a factor of 10 between different individuals." Now the CDAEP contends that a value of 10 is invalid, in direct contradiction of their statement on the preceding page. Some consistency would increase the validity and credibility of their comments. The CDAEP notes that the subjects of the Fawer study (in fact of most human studies of mercury vapour exposure) are all male. The 'healthy male' syndrome is well known. Does the CDAEP contend that we should ignore more sensitive members of the general public? This is why an uncertainty factor of 10 is routinely applied for inter-individual variation.
42	28-30	"Interestingly, the first draft of the Richardson report..."	A representative of the CDA commented on the first draft. The CDAEP review was supposed to focus on the final Richardson report. the CDAEP has criticized Richardson for not incorporating the peer review comments that it favoured. Here, the CDAEP criticize Richardson for incorporating peer review comments and advice it does not favour. Some consistency would increase the validity and credibility of their comments.
42	31-34	"According to Professor Halbach...the restriction of the TDI to mercury vapour only is not useful.."	The derivation of reference doses (TDIs) is always specific to chemical species whenever possible. This is why the U.S.EPA and ATSDR have separate reference exposure levels for mercury vapour, methylmercury and mercuric (ionic) mercury. Previous to the Richardson report, Health Canada had a TDI only for methyl mercury. They have adopted a different value for mercuric (ionic) mercury (from the U.S.EPA).
42 43	34-39 1-8	"Rather, it is reasonable ..."	The WHO ADI is cited incorrectly. That ADI does not apply to all forms of mercury, but only to methylmercury + mercuric (ionic) mercury. Also, it is totally unrelated to inhalation, the route of Hg vapour exposure, but applies only to ingestion exposure, principally because it was derived (and designed) to address risk issues relating to food (including fish) contamination. It should also be mentioned again that both Health Canada and the U.S.EPA have recently lowered their respective reference doses for methyl mercury, suggesting that the CDAEP interpretation of the pertinent data is not in agreement with that of Canadian and U.S. regulatory toxicologists.

Page	Line	CDA Comment or Criticism	Response
43	9-28	"In calculating the TUC..."	The inter-individual variation in cognitive function impairment due to mercury vapour could be calculated directly from the Echeverria data. A similar calculation could not be made for hand tremor from the Fawer data. Deriving inter-individual variability directly from the critical study in question is a superior refinement for derivation of uncertainty factors, if the data allow. The data of Langworth et al. (1988) have no bearing on the derivation of reference exposure levels. These are based on toxicological studies, not on considerations of exposure. The CDAEP continues to demonstrate a lack of understanding of the concepts, principles, and practices of regulatory risk assessment. The CDA could provide no data to Richardson on a comprehensive survey of the Canadian public respecting current (1994) dental health (number of filled teeth) or mercury levels in urine in relation to amalgam or in amalgam-free individuals. Therefore, the CDAEP can not state with any authority that the TUC of 0.7 ug/L is "already exceeded by a significant proportion of amalgam free individuals." This statement is not supported by data presented by Skerfving (1991) and others. They have no broad epidemiological data to support the statement.

Page	Line	CDA Comment or Criticism	Response
43	30-36	"It is interesting to note that...Richardson et al. (1995) are 2.81 µg/person/day ... Richardson report the average exposure was given as 3.4 ug/person/day...."	The paper by Richardson et al. (1995) was discussed in section 5.1 of the Richardson report. Estimates of exposure of adults in Richardson et al. (1995) were based on an assumed average of 7 amalgam fillings. The actual average, incorporated in the later Richardson report, is 8.65 fillings (see Table 4.1 of the Richardson report). Therefore, it is obvious that the estimated exposures presented in the Richardson report are the more accurate and should be higher given the more accurate data. Also, deterministic methods were used by Richardson et al. (1995), in which only the average or typical exposure was estimated. The probabilistic methods employed in the Richardson report incorporate the full range and frequency distribution of filled teeth in the entire Canadian population, providing a technically and statistically superior analysis of mercury exposure from dental amalgam. Interestingly, the CDAEP fails to note the difference in average number of fillings or exposure assessment methodology.
43 44	36-39 1-6	"Some confusion in toxicological terminology are apparent in the Richardson report. ...The Richardson report at times confuses the terms exposure and uptake."	Not one of 17 technically qualified invited peer reviewers of the Richardson report commented or complained about terminology. Exposure is measured as a dose. What is 'taken up' when mercury is absorbed is a dose. These terms are synonymous. The term 'uptake' generally applies to absorbed rather than delivered doses. The CDAEP appears to find confusion is terminology of common knowledge and usage within the risk assessment field, further suggesting their lack of experience and expertise in this area.
44	7-11	"Furthermore, it is inappropriate to extrapolate..."	Exposures in children and toddlers were not extrapolated from adult exposures. It is unclear what the CDAEP is referring to. They make no reference to page or equation to justify or illustrate this comment.
44	12-15	"A major error in the Richardson report is that a single key paper was selected and used for estimating unstimulated release rate..."	The unstimulated release rate was represented in this probabilistic exposure assessment as a range of values with a defined probability density function. The range of values used incorporated the range of values reported in all other studies on this issue. Contrary to the CDAEP's opinion, the paper cited was, and still is, the most thoroughly quantified investigation of unstimulated release rate. An examination of the paper by Skare and Enqvist (1994) would make this clear. Based on the studies of Vimy and Lorcheider (1985) adequate time was permitted between tooth brushing and measurement to ensure that baseline conditions prevailed.

Page	Line	CDA Comment or Criticism	Response
44	15-20	"The problem is further compounded...by the use of a magnification factor obtained almost exclusively from gum chewing...."	The magnification factor was represented in this probabilistic exposure assessment as a range of values with a defined probability density function. The range of values used incorporated the range of values reported in all other studies on this issue. Far from being an erroneous assumption, the methods and assumptions used are the most biostatistically valid representation of the full database of studies and reported magnification factors. Far from ignoring the issue of different foods, the study by Berglund (1990), the study repeatedly cited by the CDAEP on this issue, is expressly incorporated in the presentation of data and studies employed to quantify this variable. This is explicitly presented, and obvious, from figures 5.2 and 5.3 of the Richardson report. The CDAEP suggestion indicates a failure to examine these key figures and a failure to understand the methods used. Also, by suggesting that only one study (that of Berglund, 1990) be used, the CDAEP violates their own stated prerequisite of a valid risk assessment that the full database of studies must be considered.
44	20-25	"Assumptions were made regarding ... a distribution between oral and nasal breathing...it is not clear how this calculation was made."	If the calculation is not clear, it is only because the CDAEP did not read the complete report or did not understand what was presented. Valid, published scientific studies were cited regarding the rates of oral versus nasal breathing. All assumptions and equations were clearly and explicitly explained to ensure that calculations were reproducible by independent reviewers. Lack of understanding of these calculations by the CDAEP is not the result of a failure of the Richardson report to state clearly and explicitly how these calculations were performed or how variables were defined.
44	26-39	"The vast majority of release rates presented in the scientific literature ..."	The data employed and calculations made are clearly and explicitly explained in the Richardson report. Despite the criticism of studies cited, the CDA could provide no data to suggest that their comment is valid. As a result, it is imperative to rely on the available published science to formulate the risk assessment. Additional data verifying the criticism would be welcome and revisions made as appropriate. However, there are no data to verify the CDAEP's criticism and, therefore, it can only be considered speculation to be validated whenever the appropriate research is published.
44 45	39 1-8	"Furthermore, the key paper used for the conversion from the number of ...."	Practising dentists have advised Richardson that the incidence of multiple fillings in a single tooth is rare. It is very reasonable to assume that one filling equates to one filled tooth. Despite the CDAEP's speculation to the contrary, they provided no data to support their contention that this assumption is invalid. Until data verifies their position, it must be considered as unsubstantiated speculation.

Page	Line	CDA Comment or Criticism	Response
45	8-16	"The choice of this cadaver study...is also unsuitable since...We know very little about the dental status of alcoholics."	Again, the CDAEP indulges is unsubstantiated speculation as to the validity of studies cited in the Richardson report. Notably, they do not offer nor cite any data or studies to verify their speculations. This in no way invalidates the Richardson report which emphasized the use and citation of published scientific studies to quantify variables employed in the exposure assessment.
45	17-32	"When a restoration...."	Again, the CDAEP indulges is unsubstantiated speculation as to the validity of studies cited in the Richardson report. Notably, they do not offer nor cite any data or studies to verify their speculations. This in no way invalidates the Richardson report which emphasized the use and citation of published scientific studies to quantify variables employed in the exposure assessment. The CDAEP expounds on factors which increase the surface area of amalgam fillings. However, the Richardson report never used surface area as a variable, only number of amalgam filled teeth and number of amalgam surfaces per filled tooth. Therefore, this discussion is irrelevant to discussion of the Richardson report.
45 46	33-37 1-15 + Fig.2	"There are three recent studies..."	The only data that would be relevant to the Richardson report would be data that demonstrates that the number of amalgam surfaces per filled tooth increases as a function of age. However, none the three studies cited by the CDAEP present data on this relationship. An increase in total number of amalgam surfaces with age reflects the general increase in number of amalgam filled teeth with age (see Table 4.1 in Richardson report). Number of fillings and total surface area of fillings may increase with age, but this is no proof of an increase in the number of filled surfaces per filled tooth. Figure 2 in the CDAEP review is totally unrelated to any of the assumptions or variables employed in the Richardson report. Again, this is just unsubstantiated speculation are the part of the CDAEP.

Page	Line	CDA Comment or Criticism	Response
46 47	19-21 1-19	"The Richardson report used the data...cannot be considered as an unstimulated release..."	The unstimulated release rate was represented in this probabilistic exposure assessment as a range of values with a defined probability density function. The range of values used included a lower limit of 0 (zero). This range incorporated the range of values reported in all other studies on this issue. Contrary to the CDAEP's opinion, the paper cited was, and still is, the most thoroughly quantified investigation of unstimulated release rate. An examination of the paper by Skare and Enqvist (1994) would make this clear. Based on the studies of Vimy and Lorcheider (1985) adequate time was permitted between tooth brushing and measurement to ensure that baseline conditions prevailed. The stimulation reported from the Berglund paper was measured during or immediately after eating the "light meal". The measurements made by Skare and Engqvist were made an hour or more after tooth brushing, adequate time to permit baseline conditions to return.
47	20-30	"Reviewing studies where the effect of light meals... The possibility cannot be excluded..."	The CDAEP implies that human inter-individual variability in any variable, such as baseline release rate, should not exist. This is totally incorrect. Inter-individual differences obviously exist and the only valid approach to addressing this variability is to conduct a probabilistic risk assessment, as done in the Richardson report, and to define the baseline Hg release rate as a variable with a range which incorporates all published values of this variable. Again, this was done in the Richardson report. The CDAEP emphasized that all studies must be included in a valid assessment of mercury and amalgam. This is exactly what Richardson did. As in numerous previous instances, the CDAEP indulges in unsubstantiated speculation in order to imply that the Skare and Enqvist paper is somehow invalid. Speculation can not be considered valid criticism.

Page	Line	CDA Comment or Criticism	Response
47 49 50	31-37 1-37 1-17	"The equation for the regression line in Skare and Enqvist (1994) study was:..."	Richardson can only repeat that the manner in which the unstimulated release rate was defined in the Richardson report was as a probability density function which spanned the range of all published accounts of baseline Hg release rate, including 0 (zero). This is amply obvious in the Richardson report. The CDAEP implies that human inter-individual variability in any variable, such as baseline release rate, should not exist. This is totally incorrect. Inter-individual differences obviously exist and the only valid approach to addressing this variability is to conduct a probabilistic risk assessment, as done in the Richardson report, and to define the baseline Hg release rate as a variable with a range which incorporates all published values of this variable. Again, this was done in the Richardson report. The CDAEP emphasized that all studies must be included in a valid assessment of mercury and amalgam. This is exactly what Richardson did. The CDAEP, to follow their own prerequisite, should insist that the quantification of the baseline release rate should encompass all published studies, as done in the Richardson report, and not ignore or omit certain studies, as done by the CDAEP. As in numerous previous instances, the CDAEP indulges in unsubstantiated speculation in order to imply that the Skare and Enqvist paper is somehow invalid. Speculation can not be considered valid criticism.
50 55	18-38 1-19	"5.1.3. Stimulation Magnification Factor: ..."	This entire section clearly points out the inter-individual variation in this factor and the CDAEP is suggesting that the full database of studies on this variable not be considered, in violation of their own stated prerequisite that all studies be considered. The magnification factor was represented in this probabilistic exposure assessment as a range of values with a defined probability density function. The range of values used incorporated the range of values reported in all available studies on this issue, including no (zero) magnification. Far from being an erroneous assumption, the methods and assumptions used are the most biostatistically valid representation of the full database of studies and reported magnification factors. Far from ignoring the issue of different foods, the study by Berglund (1990), the study repeatedly cited by the CDAEP on this issue, is expressly incorporated in the presentation of data and studies employed to quantify this variable. This is explicitly presented, and obvious, from figures 5.2 and 5.3 of the Richardson report. The CDAEP suggestion indicates a failure to examine these key figures and a failure to understand the methods used.

Page	Line	CDA Comment or Criticism	Response
55	26-31	"The Richardson report has assumed that all chewing and tooth brushing results in a maximum stimulated release.."	The CDAEP implies that the Richardson model assumed that the maximum stimulated release (stimulation magnification factor) was a single high value in all cases. This is totally false. The stimulation magnification factor was designed to randomly vary from a lowest value of 0 (i.e., no stimulation at all despite eating, tooth brushing, etc.), to a high of about 20. Therefore, it is clearly evident that the Richardson report did not assume that individual tooth brushing events or eating events resulted in the maximum stimulation magnification factor of 20. Experience in biostatistics and risk assessment would have made this readily evident. The geometric mean is not erroneous. As is readily apparent from an inspection of Figure 5.3, the probability density function describing the distribution of these data reflects an excellent statistical fit.
55 56	31-38 1-5 + Fig. 5	"The release during ... but no build-up phase has been used as in the original study."	Richardson is pleased to see the CDAEP citing the Vimy and Lorscheider (1985) study as the most appropriate study to define the buildup and decay of stimulated Hg release from amalgam. The CDAEP is totally incorrect in their interpretation of the Vimy and Lorscheider data. The Vimy and Lorscheider paper does not report data on a gradual increase in the stimulated Hg rate. It indicates a gradual increase in the concentration of Hg in the mouth. An understanding of their research would make this apparent. A gradual increase in the concentration of Hg in the air of the mouth is expected because of the dilution offered by volume of uncontaminated air in the mouth. With stimulated Hg release at a constant rate, and the volume of air in the oral cavity being constant, the concentration of Hg in the mouth will start at zero and increase with time. This is analogous to pouring salt at a constant rate into a glass of water. The concentration of salt in the water after 2 minutes is greater than the concentration after only 1 minute, despite a constant rate of pouring salt.

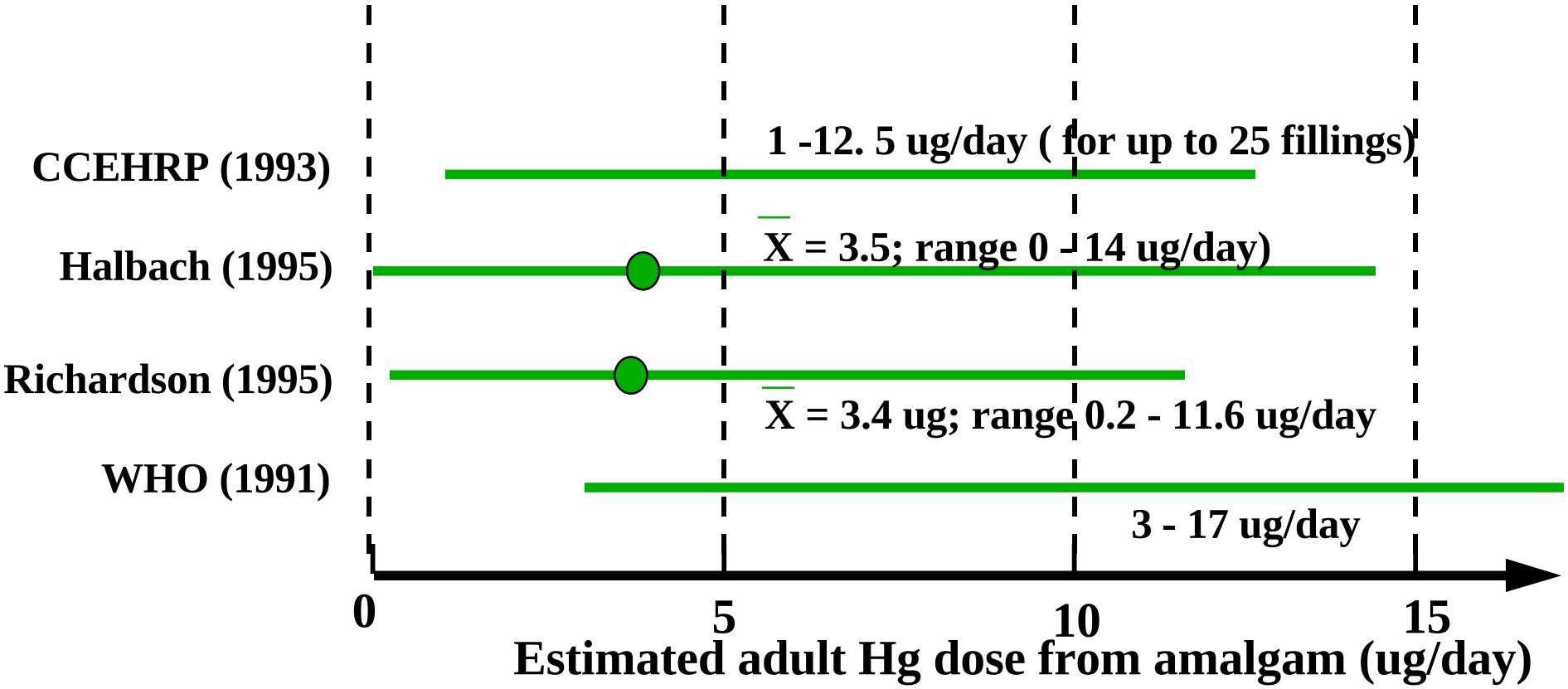
Page	Line	CDA Comment or Criticism	Response
56 57		5.1.5 Ingestion Absorption Factor	Richardson is surprised at the CDAEP's comments. Both the WHO and the ATSDR acknowledge the Rahola et al. (1973) study regarding absorption of mercuric nitrate in humans at a rate of 15%. The Richardson report, in fact, acknowledges that the range of absorption from the GI tract is between 5 and 15%, as dictated by the published data. This is in no way inconsistent with the WHO which concluded that an average rate of absorption of mercuric chloride may be 7%, not the maximum. It is essential to acknowledge the inter-individual variability in Hg absorption rate in order to establish valid population-based estimates of mercury exposure. It is also essential to acknowledge that not all mercuric mercury will be in the form of $HgCl_2$ but that other chemical forms are possible, particularly from biological tissues such as foods. Peer reviewers with expertise in mercury toxicity and pharmacokinetics, including T. Clarkson and R. Canady (ATSDR), failed to note any error in this variable.

Page	Line	CDA Comment or Criticism	Response
57 59		5.2 Validity of the Exposure Assessment	The test for validity, as attempted by the CDAEP, is itself invalid. These data can not be applied to a single limited study, such as the Berglund (1990) study, as it was limited in sample size and scope. Validity is best measured in terms of how the exposure estimates of the Richardson report compare with other published studies considered valid by the CDAEP. The CDAEP has stated that the exposure estimates of the U.S.DHHS, in the CCEHRP (1993) report, are the most valid. The CDAEP has also quoted liberally from Dr. Stefan Halbach with respect to risk assessment so Richardson must assume that they admire Halbach's work and consider it valid. The estimates of exposure to mercury from amalgam presented in the Richardson report, in the CCEHRP (1993) report, and those determined by Dr. Stefan Halbach (Halbach, 1995) are virtually identical (see attached figure). The CCEHRP indicates that a person with 7 to 10 amalgam fillings receives 1 to 5 ug/day. For a person with 25 filled teeth, the maximum reported in Canada, then the daily exposure would be 1 to 12.5 ug/day. Habach (1995) estimated an average of 3.4 to 4.5 ug/day (dependent on measurement method) for persons with up to 48 amalgam surfaces. Assuming an average of 2 surfaces per filled tooth, then this equates to about 24 filled teeth. For up to 25 filled teeth, the Richardson report estimated from 0.2 to 11.6 ug/day, with an average of 3.4 ug/day, virtually identical compared to CCEHRP (1993) and Halbach (1995). Other estimates presented by Weiner and Nylander (1995), Skare and Engqvist (1994) are also similar in magnitude. The WHO (1991) suggested a range of exposure from 3 to 17 ug/day. This is also similar, albeit somewhat higher, than in the Richardson report, CCEHRP (1993), and Halbach (1995). As a result, it is readily apparent that CCEHRP (1993), Halbach (1995) and Richardson, along with others, agree on the range of Hg exposure arising in the population from amalgam. As the CDAEP accepts the estimates of CCEHRP, and must accept Halbach's estimates of exposure, given that they have sought out and quoted his advice regarding risk assessment of mercury exposure, then they must also accept the exposure estimates of Richardson.

Page	Line	CDA Comment or Criticism	Response
57 59		5.2 Validity of the Exposure Assessment	This point is further validated by an examination of a paper by Eley (1997), a member of the CDAEP. In the article in volume 182 of the British Dental Journal, Eley displays a table (Table VIII) of data which he attributes to Richardson and which he claims is in error. He then displays a table (Table IX) of data which he attributes to Mackert and which he claims is the correct data. Interestingly, the data for Hg exposure from amalgam presented in Table VIII and attributed to Richardson do not come from the Richardson report. The data in Table IX on total Hg exposure and amalgam exposure, attributed to Mackert, are in fact from the Richardson report. Therefore, a member of the CDAEP supports the estimated exposures presented in the Richardson report.
60	9-16	"In addition the WHO EHC 118 (1991) ...an increasing number of amalgam fillings there was a rise of mercury level in urine. Interestingly the reason for this is not known, one possible explanation is the non-linear metabolism of inorganic mercury".	In fact, the reason for this logarithmic increase in urinary Hg concentration with increasing amalgam load is known. As explained by Richardson (1998), the proportion of total, absorbed Hg vapour excreted in urine increases as daily dose increases. This produces the curvilinear relationship of urine mercury concentration with amalgam load observed by Skerfving (1991), Herrmann and Schweinsberg (1993), Langworth *et al.* (1988, 1991), and Akesson *et al.* (1991). In fact, Richardson was commissioned by the Swedish Council for the Planning and Coordination of Research in 1998 to re-evaluate the Richardson report in light of this new knowledge. Estimated exposures were slightly higher than predicted in the Richardson report when this factor was considered. Also, unlike the data of Berglund and Berglund and Molin, only those studies investigating mercury in urine as a function of amalgam load with sufficient sample sizes will be able to detect this curvilinear relationship and thereby be considered valid for predictive purposes. Those studies include Skerfving (1991), Herrmann and Schweinsberg (1993), Langworth *et al.* (1988, 1991), and Akesson *et al.* (1991). Both the Berglund and Berglund and Molin studies included insufficient samples sizes (total N=32 with both studies combined) to be considered anything other than qualitative in nature.
62		"...Fawer et al. (1983)...	The CDAEP is suggesting here that a dose associated with 26 ug Hg/m^3, an exposure known to cause CNS impairment (ATSDR, 1994; U.S.EPA, 1998; Richardson and Allan, 1996), is safe for people with amalgam. If this were true, Health Canada surely would not have recommended restrictions in amalgam use in children, pregnant women, people with kidney disease, etc. The calculations presented by the CDAEP are totally erroneous.

Page	Line	CDA Comment or Criticism	Response
64	7.0	Conclusions	This paragraph is ostensibly the CDA's political position on the amalgam issue. Despite their repeated claim that amalgam is safe, they recommend that funding be made available from government to further investigate any concerns and questions surrounding the safety of dental amalgam. Wouldn't funding be unnecessary if amalgam were actually as safe as the CDAEP has tried to suggest? This request for funding is in total contradiction to their claim of safety. It appears to be a direct admission that they can not answer all the concerns and questions surrounding amalgam as they have implied in their review.

Figure: Range of mercury exposures predicted by CCEHRP (1993), Richardson (1995) and WHO (1991). It is readily apparent that these three independent evaluations of exposure all arrived at the same general answer, within reasonable (and very limited) variation. If any one of these estimates is valid, then they all must be valid.



10.0 References

Agency for Toxic Substances and Disease Registry. 1994. Toxicological Profile for Mercury (Update). U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. 357p. + appendices.

Akesson, I., Schutz, A., Attewell, R. *et al.* 1991. Status of mercury and selenium in dental personnel: impact of amalgam work and own fillings. Arch. Environ. Health, 46(2): 102-109.

Albers, J.W., L.R. Kallenbach, L.J. Fine, et al. 1988. Neurological abnormalities associated with remote occupational elemental mercury exposure. Ann. Neurol., 24: 651-659.

American Conference of Governmental Industrial Hygienists (ACGIH). 1997. 1997 TLVs and BEIs. ACGIH, Cincinnati.

Andersen, A., D.G. Ellingsen, T. Morland, H. Kjuus. 1993. A neurological and neurophysiological study of chloralkali workers previously exposed to mercury vapour. Acta Neurol. Scand., 88: 427-433.

Anger, W.K. and O.J. Sizemore. 1993. Adult environmental neurobehavioural test battery (AENTB), examiner training manual. ATSDR, report 2ATSDR/2621.

Aposhian, H.V., Bruce, D.C., Alter, W. *et al.* 1992. Urinary mercury after administration of 2,3-dimercaptopropane-1-sulfonic acid: correlation with dental amalgam score. FASEB J., 6: 2472-2476.

Aronsson, A.M., B. Lind, M. Nylander and M. Nordberg. 1989. Dental amalgam and mercury. Biology of Metals 2:25-30.

Barregard, L., B. Hultberg, A.Shutz and G.Sallsten. 1988. Enzymuria in workers exposed to inorganic mercury. Int. Arch. Occup. Environ. Health, 61: 65-69.

Berglund, A. 1990. Estimation by a 24-hour study of the daily dose of intra-oral mercury vapor inhaled after release from dental amalgam. J. Dent. Res., 69(10): 1646-1651.

Berglund, A. and M. Molin. 1996. Mercury vapour release from dental amalgam in patients with symptoms allegedly caused by amalgam fillings. Eur. J. Oral. Sci., 104: 56-63.

Boogaard, P.J., A.-T.A.J. Houtsma, H. L. Journée and N.J. van Sittert. 1996. Effects of exposure to elemental mercury on the nervous system and the kidneys of workers producing natural gas. *Arch. Environ. Health*., 51(2), 108-115.

Boyd, N.D., H. Benediktsson, M.J. Vimy, D.E. Hooper and F.L. Lorscheider. 1991. Mercury from dental silver tooth fillings impairs sheep kidney function. Am J. Physiol., 261: R 1010-R 1014.

Cardenas, A., Roels, H., Bernard, A.M., Barbon, R., Buchet, J.P., Lauwerys, R.R., Rosello, J., Hotter, G. 1993. Markers of early renal changes induced by industrial pollutants. I. Application to workers exposed to mercury vapour. Br. J. Indust. Med., 50: 17-27.

Cavalleri, A., L. Belotti, F. Gobba, G. Luzzana, P. Rosa and P. Seghizzi. 1995. Colour vision loss in workers exposed to elemental mercury vapour. *Toxicol. Let*., 77, 351-356.

Cianciola, M.E., D. Echeverria, M.D. Martin, H.V. Aposian and J.S. Woods. 1997. Epidemiologic assessment of measures used to indicate low-level exposure to mercury vapor (Hg^0). J. Toxicol. Environ. Health, 52: 19-33.

Committee to Coordinate Environmental Health and Related Programs (CCEHRP). 1993. Dental amalgam: a scientific review and recommended Public Health Service strategy for research, education and regulation. Department of Health and Human Services, Public Health Service, Washington, D.C. 28 p. + appendices.

Drasch, G., Schupp, I., Hofl, H. *et al.* 1994. Mercury burden of human fetal and infant tissues. Eur. J. Pediatr., 153: 607-610.

Echeverria, D., Heyer, N.J., Martin, M.D., Naleway, C.A., Woods, J.S., Bittner, A.C.Jr. 1995. Behavioral effects of low-level exposure to Hg^0 among dentists. Neurotoxicol. Teratol., 17(2): 161-168.

Echeverria, D., H. V. Aposhian, J.S. Woods, et al. 1998. Neurobehavioral effects from exposure to dental amalgam Hg^0: new distinctions between recent exposure and Hg body burden. In: Amalgam Frågan, FORSKNINGSRÅDSNÄMNDEN (FRN), Stockholm, Sweden, February, 1998.

Eley, B.M. 1997. The future of dental amalgam: a review of the literature, part 4: mercury exposure hazards and risk assessment. Brit. Dent. J., 182(10): 373-381.

Ellingsen, D.G., T. Morland, A.Andersen, and H. Kjuus. 1993. Relation between exposure related indices and neurological and neurophysiological effects in workers previously exposed to mercury vapour. Brit. J. Indust. Med., 50: 736-744.

Englund, G.S., Dahlqvit, R., Lindelof, B. *et al.* 1994. DMSA administration to patients with alleged mercury poisoning from dental amalgams: a placebo-controlled study. J. Dent. Res., 73(3): 620-628.

Eti, S. R. Weisman, R. Hoffman and M.M. Reidenberg. 1995. Slight renal effect of mercury from amalgam fillings. *Pharmacol. Toxicol*., 76, 47-49.

Fawer, R.F., de Ribaupeirre, Y., Buillemin, M.P. *et al.* 1983. Measurement of hand tremor induced by industrial exposure to metallic mercury. Br. J. Ind. Med., 40: 204-208.

Godfrey, M.E. 1990. Chronic illness in association with dental amalgam: report of two cases. J. Adv. Med., 3: 247-255.

Gonzalez-Ramirez, D., Maiorino, R.M., Zuniga-Charles, M. *et al.* 1995. Sodium 2,3-dimercaptopropane-1-sulfonate challenge test for mercury in humans: II. urinary mercury, porphyrins and neurobehavioral changes of dental workers in Monterrey, Mexico. J. Pharmacol. Exper. Therap., 272(1): 264-274.

Günther, W., B. Sietman and A. Seeber. 1996. Repeated neurobehavioral investigations in workers exposed to mercury in a chloralkali plant. *Neurotoxicol*., 17(3-4), 605-614.

Halbach, S. 1995. Estimation of mercury dose by a novel quantitation of elemental and inorganic species released from amalgam. Int. Arch. Occup. Environ. Health, 67: 295-300.

Hann, H.J., Gray, A.S., Yeo, D.J. *et al.* 1984. A dental health survey of British Columbia children. J. Can. Dent. Assoc., 50(10). 754-759.

Health Canada (HC). 1994. Human Health Risk Assessment for Priority Substances. Canadian Environmental Protection Act Report, Supply and Services Canada, Ottawa. 36p.

Herrmann, M., Schweinsberg, F. 1993. [Biomonitoring and evaluation of mercury burden from amalgam fillings: mercury analysis in urine without and after oral gavage of 2,3-dimecapto-1-propane sulfonic acid (DMPS) and in hair]. Zbl. Hyg., 194: 271-291. (German with english summary).

International Agency for Research on Cancer. 1993. IARC Monograms on the Evaluation of Carcinogenic Risks to Humans, Volume 58: beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. IARC, WHO, Lyon, France.

Johnston, D.W., Grainger, R.M., Ryan, R.K. 1986. The decline of dental caries in Ontario school children. J. Can. Dent. Assoc., 52(5): 411-417.

Jokstad, A., Thomassen, Y., Bye, E. *et al.* 1992. Dental amalgam and mercury. Pharmacol. Toxicol. 70: 308-313.

Kishi, R., R. Doi, Y. Fukuchi, H. Satoh, et al. 1993. Subjective symptoms and neurobehavioral performances of ex-mercury miners at an average of 18 years after the cessation of chronic exposure to mercury vapor. Environ. Res., 62: 289-302.

Langworth, S., Elinder, C-G., Gothe, C-J *et al.* 1991. Biological monitoring of environmental and occupational exposure to mercury. Int. Arch. Occup. Environ. Health, 63: 161-167.

Langworth, S. Almkvist, O., Soderman, E. *et al.* 1992b. Effects of occupational exposure to mercury vapour on the central nervous system. Br. J. Ind. Med., 49: 545-555.

Langworth, S., Kolbeck, K-G, Akesson, A. 1988. Mercury exposure from dental fillings. II. release and absorption. Swed. Dent. J., 12: 71-72.

Langworth, S. Elinder, C.G., Sundquist, K.G. *et al.* 1992a. Renal and immunological effects of occupational exposure to inorganic mercury. Br. J. Ind. Med., 49: 394-401.

Langworth, S., G. Sällsten, L. Barregård, I. Cynkier, M.-L. Lind and E. Söderman. 1997. Exposure to mercury vapor and impact on health in the dental profession in Sweden. *J. Dent. Res*., 76(7), 1397-1404.

Levine, S.P., Cavender, G.D., Langolf, G.D. *et al.* 1982. Elemental mercury exposure: peripheral neurotoxicity. Br. J. Indust. Med., 39: 136-139.

Levy, M. 1995. Dental amalgam: toxicological evaluation and health risk assessment. J. Can. Dent. Assoc., 61(8): 667-674.

Liang, Y-X., Sun, R-K. Sun, Y. *et al.* 1993. Psychological effects of low exposure to mercury vapour: application of a computer-administered neurobehavioral evaluation system. Environ. Res., 60: 320-327.

Lipfert, F.W., P.D. Moskowitz, et al., 1994. Assessment of mercury health risks to adults from coal combustion. Special report from Biomedical and Environmental Assessment Group, Analytical Sciences Division, Brookhaven National Laboratory, Upton, Long Island, New York.

Lizaire, A.L., Hargreaves, J.A., Finnigan, P.D. *et al.* 1987. Oral health status of 13-year-old school children in Alberta, Canada. J. Can. Dent. Assoc., 53(11): 845-848.

Lob, M. 1965. Intoxications chronique par le mercure dans l'industrie des tubes luminescent. Archives des maladies provessionnelles de mèdicine du travail et de sécurité sociale. 26: 289-292.

Magos, L. 1991. Mercury metabolism and toxicology. In: Horsted-Bindslev, P., L. Magos, et al. (eds). Dental amalgam - a health hazard? Munksgaard, Copenhagen.

Marek, M. 1992. Interactions between dental amalgams and the oral environment. Adv. Dent. Res., 6: 100-109.

Mason, H.J. and Calder, I.M. 1994. The correction of Urinary mercury concentrations in untimed, random urine samples. Occup. Environ. Med., 51: 287.

Ngim, C-H., Foo, S.C., Boey, K.W. *et al.* 1992. Chronic neurbehavioral effects of elemental mercury in dentists. Br. J. Ind. Med., 49(11): 782-790.

Nimmo, A. M.S. Werley, J.S. Martin and M.F. Tansy. 1990. Particulate inhalation during the removal of amalgam restorations. J. Prosthet. Dent., 63: 228-233.

Nuyts, G.D., H.A. Roels, G.F. Verpooten, A.M. Bernard, R.R. Lauwerys and M.E. de Broe. 1992. Intestinal-type alkaline phosphatase in urine as an indicator of mercury induced effects on the S3 segment of the proximal tubule. *Nephrol. Dial. Transplant*, 7, 225-229.

Olsson, S., Bergman, M. 1992. Daily dose calculations from measurements of intra-oral mercury vapor. J. Dent. Res., 71(2): 414-423.

Payette, M., Plante, R., L'Heureux, J-B. 1988. Comparison of dental caries and oral hygiene indices for 13-14 year old Quebec children between 1977 and 1984. J. Can. Dent. Assoc., 54(3): 183-190.

Piikivi, L., Hanninen, H. 1989. Subjective symptoms and psychological performance of chlorine-alkali workers. Scand. J. Work Environ. Health, 15: 69-74.

Piikivi, L. and A. Ruokonen. 1989. Renal function and long-term low mercury vapor exposure. *Arch. Environ. Health*, 44(3), 146-149.

Piikivi, L., Tolonen, U. 1989. EEB findings in chlor-alkali workers subjected to low long term exposure to mercury vapour. Br. J. Ind. Med., 46(6): 370-375.

Rahola, T., T.Hattula, A. Korolainen, et al. 1973. Elimination of free and protein-bound ionic mercury $_{203}Hg^{2+}$ in man. Ann. Clin. Res., 5: 214-219.

Ratcliffe, H.E., G.M. Swanson and L.J. Fischer. 1996. Human exposure to mercury: a critical assessment of the evidence of adverse health effects. *J. Toxicol. Environ. Health*, 49, 221-270.

Richards, J.M. and P.J. Warren. 1985. Mercury vapour released during the removal of old amalgam restorations. Brit. Dent. J., 159 (7): 231-232

Richardson, G.M. 1995. *Assessment of Mercury Exposure and Risks from Dental Amalgam. Final Report*. Medical Devices Bureau, Health Canada, Ottawa. 109p.

Richardson, G. M. 1996. Deterministic versus Probabilistic Risk Assessment: Strengths and Weaknesses in a Regulatory Context. *Human and Ecological Risk Assessment*, 2, 1, 44-54.

Richardson, G.M. Mitchell, M. Coad, S. *et al.* 1995. Exposure to mercury in Canada: a multimedia analysis. Water, Air Soil Pollut. J., 80: 21-30.

Richardson, G.M. and M. Allan. 1996. A Monte Carlo Assessment of Mercury Exposure and Risks from Dental Amalgam. *Human and Ecological Risk Assessment*, 2(4):709-761.

Richardson, G.M. 1998. Mercury Exposure from Dental Amalgam: Re-evaluation of the Richardson Model, Standardization by Body Surface Area, and Consideration of Recent Occupational Studies. In: Amalgam Frågan, FORSKNINGSRÅDSNÄMNDEN (FRN), Stockhom, Sweden, February, 1998.

Ritchie, K.A., E.B. Macdonald, R. Hammersley, J.M. O'Neil, D.A. McGowan, I.M. Dale and K. Wesnes. 1995. A pilot study of the effect of low level exposure to mercury on the health of dental surgeons. *Occup. Environ. Med.*, 52, 813-817.

Roels, H., Lauwerys, R., Buchet, J.P. *et al.* 1982. Comparison of renal function and psychomotor performance in workers exposed to elemental mercury. Int. Arch. Occup. Environ. Health, 50: 77-93.

Roels, H., Abdeladim, S., Ceulemans, E. *et al.* 1987. Relationships between the concentrations of mercury in air and in blood or urine of workers exposed to mercury vapor. Ann. Occup. Hyg., 31(2): 135-145.

Roels, J., Gennart, J-P, Lauwerys, R. *et al.* 1985. Surveillance of workers exposed to mercury vapour: validation of a previously proposed biological threshold limit value for mercury concentration in urine. Am. J. Ind. Med., 7: 45-71.

Roels, H., S. Abdeladim, M. Braun, J. Malchaire and R. Lauwerys. 1989. Detection of hand tremor in workers exposed to mercury vapor: a comparative study of three methods. *Environ. Res*., 49, 152-165.

Rowland, A.S., Baird, D.D, Weinberg, C.R. *et al.* 1994. The effect of occupational exposure to mercury vapour on the fertility of female dental assistants. Occup. Environ. Med., 51: 28-34.

Sallsten, G., Barregard, L., Osterberg, T. 1991. Tandgnissling hos amalgambarare - en orsak till hog kvicksilverutsondring? [Bruxism in amalgam bearers - a cause of high mercury excretions?]. Lakartidningen, 88(4): 232-233.

Schuckmann, F. 1979. Study of preclinical changes in workers exposed to inorganic mercury in chloralkali plants. Int. Arch. Occup. Environ. Health, 44: 193-200.

Shapiro, I.M., Cornblath, D.R., Sumner, A.J. *et al.* 1982. Neurophysiological and neuropsychological function in mercury-exposed dentists. The Lancet, May 22, 1982: 1147-1150.

Singer, R., Valciukas, J.A., Rosenman, K.D. 1987. Peripheral Neurotoxicity in workers exposed to inorganic mercury compounds. Arch. Environ. Health, 42(4): 181-184.

Skare, I., Engqvist, A. 1994. Human exposure to mercury and silver released from dental amalgam restorations. Arch. Environ. Health, 49(5): 384-394.

Skerfving, S. 1991. Exposure to mercury in the population. In: Advances in Mercury Toxicology, Suzuki *et al.* (eds)., Plenum Press, New York.

Smith, A.E., P.B. Ryan and J.S. Evans. 1992. The effect of neglecting correlations when propagating uncertainty and estimating the population distribution of risk. Risk Anal., 12(4): 467-474.

Suzuki, T., Hongo, T, Abe, T. *et al.* 1993. Urinary mercury level in Japanese school children: influence of dental amalgam fillings and fish eating habits. Sci. Tot. Environ., 136: 213-227.

Svare, C.W., L.C. Peterson, J.W. Reinhardt, D.B. Boyer, C.W. Frank, D.D. Gay and R.D. Cox. 1981. The effect of dental amalgams on mercury levels in expired air. Journal of Dental Research 60:1668-1671.

Svensson, B-G., Schutz, A., Nilsson, A. *et al.* 1992. Fish as a source of exposure to mercury and selenium. Sci. Tot. Environ., 126: 61-74.

U.S. Department of Health and Human Services (USDHHS). 1987. Oral Health of United States Adults: National Findings. National Institute for Dental Research, National Institute of Health Publication no. 87-2868.

U.S. EPA (U.S. Environmental Protection Agency). 1998. *Integrated Risk Information System (IRIS)*. Online. National Center for Environmental Assessment, Cincinnati, OH.

Uzzell, G.P., Oler, J. 1986. Chronic low-level mercury exposure and neuropsychological functioning. J. Clin. Exper. Neuropsych., 8(5): 581-593.

Verberk, M.M., Salle, H.J.A., Kemper, C.H. 1986. Tremor in workers with low exposure to metallic mercury. Am. Ind. Hyg. J. 47(8): 559-562.

Vimy, M.J. 1996. Mercury usage in Canadian Dentistry: Part 2: The CDA's International Dental Expert Panel on Amalgam. Report submitted to Health Canada, February, 1996.

Vimy, M.J., and F.L. Lorscheider. 1985. Serial measurements of intra-oral air mercury: estimation of daily dose from dental amalgam. Journal of Dental Research 64(8):1072-1075.

Weiner, J.A. and Nylander, M. 1995. An estimation of the uptake of mercury from amalgam fillings based on urinary excretion of mercury in Swedish subjects.. *Sci. Tot. Environ.*, 168, 255-265.

Wolff, M., J.W. Osborne and A.L. Hanson. 1983. Mercury toxicity and dental amalgam. Neurotoxocol., 4(3): 201-204.

Woods, J.S., Martin, M.D., Naleway, C.A, Echeverria, D. 1993. Urinary porphyrin profiles as a biomarker of mercury exposure: studies on dentists with occupational exposure to mercury vapor. J. Toxicol Environ. Health, 40: 235-246.

World Health Organization. 1990. Methylmercury. Environmental Health Criteria 101. International Program on Chemical Safety, Geneva. 144p.

World Health Organization. 1991. Inorganic mercury. Environmental Health Criteria 118. International Programme on Chemical Safety, Geneva. 168p.