ASSESSMENT OF MERCURY EXPOSURE AND RISKS FROM DENTAL AMALGAM

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FINAL REPORT

Executive Summary

For Canadians with amalgam-filled teeth, it was estimated that total mercury (Hg) exposure averages: 3.3 μg Hg/day in toddlers (aged 3 to 4 years); 5.6 μg Hg/day in children (aged 5 to 11 years); 6.7 μg Hg/day in teens (aged 12 to 19 years); 9.4 μg Hg/day in adults (aged 20 to 59 years); and 6.8 μg Hg/day in seniors (aged 60+ years). Of this exposure, amalgam was estimated to contribute 50% to total Hg exposure in adults, and 32 to 42% for other age groups. Estimates, based on two independent models, of exposure from amalgam alone were: 0.8 - 1.4 μg Hg/day in toddlers; 1.1 - 1.7 μg Hg/day in children; 1.9 - 2.5 μg Hg/day in teens; 3.4 - 3.7 μg Hg/day in adults; and 2.1 - 2.8 μg Hg/day in seniors.

There are insufficient published data on the potential health effects of dental amalgam specifically to support or refute the diverse variety of health effects attributed to it. Numerous studies constantly report effects on the central nervous system (CNS) in persons occupationally exposed to Hg. Virtually all studies failed to detect a threshold for the effects CNS measured. A tolerable daily intake (TDI) of 0.014 μg Hg/kg body weight/day was proposed for mercury vapour, the principal form of mercury to which bearers of amalgam fillings are exposed. This TDI was based on a published account of sub-clinical (i.e. not resulting in overt symptoms or medical care) CNS effects in occupationally exposed men, expressed as slight tremor of the forearm. An uncertainty factor of 100 was applied to these data, to derive a reference dose (TDI) which should, in all probability, prevent the occurrence of CNS effects in non-occupationally-exposed individuals bearing amalgam fillings.

The number of amalgam-filled teeth, for each age group, estimated to cause exposure equivalent to the TDI were: 1 filling in toddlers; 1 filling in children; 3 fillings in teens; and 4 fillings in adults and seniors. It was recognized that filling size and location (occlusal versus lingual or buccal) may also contribute to exposure. However, data suggest that no improvement in prediction of exposure is offered by any particular measure of amalgam load. Therefore, the estimates of exposure derived from the number of filled teeth were considered as reliable as those that might be based on size and position of amalgam fillings, were such data available for the Canadian population.

Effects caused by allergic hypersensitivity to amalgam or mercury, including possible auto-immune reactions, can not be adequately addressed by any proposed tolerable daily intake. Individuals suspecting possible allergic or auto-immune reactions should avoid the use of amalgam by selecting suitable alternate materials in consultation with dental care (and possibly health care) professionals.

Preface

This report has been prepared in response to concerns that exposure to mercury from dental amalgam may adversely impact on health. Recent reviews (USDHHS 1993, Swedish National Board of Health, 1994) have concluded that there is no evidence to suggest that dental amalgam, specifically, is injurious to health. However, the data base relating health impacts in humans or animals to amalgam specifically is small and weak. This suggests that indirect evidence relating mercury vapour exposure (the predominant form of mercury released by dental amalgam) to human health effects (for which a large data base exists) is a necessary basis for an evaluation of the possible health risks of dental amalgam. In the reports previously mentioned, exposure to mercury arising from amalgam was not adequately quantified, and a level of mercury vapour exposure which is, in all probability, tolerable to the vast majority of persons bearing amalgam fillings, was not defined. This report attempts to address these previous deficiencies.

This report is not exhaustive. Recent reviews on mercury (WHO 1990, 1991; IARC 1993; ATSDR 1994) adequately review many aspects of mercury toxicity and exposure. Instead, this report focuses on studies which report on health effects in dental care practitioners and other occupational groups exposed to relatively low levels of mercury. This report also examines recent research which hypothesizes a link between mercury exposure, and thereby dental amalgam, and Alzheimer's Disease. This report concentrates on effects associated with long term mercury vapour exposure (via inhalation) in humans. Other reviews (WHO 1990, 1991; IARC 1993; ATSDR 1994) examined acute and sub-chronic toxicity of mercury vapour in humans and animals, chronic toxicity of mercury vapour exposure in animals, and all aspects of the toxicology of exposure to other forms of mercury via other routes of exposure (ingestion, dermal absorption), in extensive and adequate detail such that this is not repeated here.

Any medical or dental material, such as amalgam, will have associated with it some degree of health risk. The purpose of this report is to attempt some determination of what that risk is (i.e. what effect(s) it may cause), how significant it is (i.e. what level of exposure should be free from effect), and what proportion of the population might be at some degree of risk (i.e. how many exceed the level considered to be free from effect).

Acknowledgements

The author extends his appreciation to Ms. M. Allan, Cornerstone Engineering and Consulting Inc., Calgary, Alberta, for undertaking the assessment of exposure after the model of Olsson and Bergman (1992) (see section 5.2). This contribution ensured that the two exposure models presented were wholly independent.

Peer review

Extensive peer review was undertaken on the first draft of this report. Comments and criticisms were provided by 7 persons active in academic, health, and dental sciences and risk assessment research, many specifically investigating mercury or amalgam. Also, 9 persons involved in environmental and dental material regulation provided comments. Peer reviewers have not been identified to ensure that it is not construed that they agree with the report or its conclusions.

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1.0 Introduction

Amalgam has been used in dental practice since the 1800's (USDHHS, 1993; Lorscheider et al. 1995). Current formulations contain 43 to 50.5% mercury (Hg) by weight mixed with an alloy containing silver (40 to 70%), tin (12 to 30%), copper (12 to 30%), indium (0 to 4 %), palladium (0.5%) and zinc (0 to 1%) (Berry et al. 1994). Since its inception into use, there has been controversy over the safety of dental amalgam, due to its Hg content. Major debates arose during its first introduction, again in the 1920's and 1930's and, lately, since the 1980's (reviewed by Goldwater, 1972; Molin, 1992; and others).

Frykholm (1957) suggested that exposure occurred in the dental patient for only a short period following placement of a filling, but that this exposure decreased and ended soon after. This has also been reported more recently (Haikel et al., 1990). However, the vast majority of recent studies (Gay et al. 1979; Svare et al., 1981; Patterson et al. 1985; Vimy and Lorscheider, 1985a; Berglund et al. 1988; Jokstad et al. 1992; and others) demonstrate that Hg is released from dental amalgam fillings continuously over their lifetime, resulting in continuous exposure.

The use of Hg-containing amalgam for over 150 years with no apparent 'epidemic' of ill effects has been espoused as evidence of the safety of dental amalgam (Jones, 1993; also discussed by Lorscheider et al. 1995). However, this position assumes that the medical research community was fully aware of and pursuing research in this area, that significant effects could be detected with the methods available, and that a regular and systematic effort was made to detect such effects. The very sporadic nature of the amalgam debate, the relatively recent introduction of this issue to the health sciences research community (Lorscheider et al. 1995), and the development, only recently, of more sensitive methods for detecting psychologic, neurologic, immunologic and renal effects indicates that these three assumptions are not likely true.

There is a growing body of anecdotal reports of illness attributed to dental amalgam, as evidenced by reports of adverse reactions submitted by individuals to Health Canada. This increase in submissions is due, in part, to the increased recent publicity surrounding this issue. However, the cessation or reduction of illness has been reported in association with the removal of amalgam fillings (Godfrey 1990), although the database is insufficient to distinguish between actual and possible plecebo effect (Swedish National Board of Health, 1994).

There is considerable debate and controversy as to the validity of reports of illness associated with dental amalgam (Weiner et al. 1990; Molin 1992; Eley and Cox 1993; Berry et al. 1994; and others). Their onset has been attributed to psychosomatic factors (Swedish National Board of Health, 1994), and the remission or elimination of effects following amalgam removal has been attributed to placebo effect (Englund et al. 1994). However, there have been no properly controlled and conducted clinical investigations that provide unequivocal data to support or refute health hazards attributed to this dental material. Despite

the recognition of the lack of adequate clinical studies as early as 1931 (Souder and Sweeney 1931), again in 1987 (Enwonwu 1987), and in 1990 (Weiner et al. 1990), appropriate studies have not been initiated by dental practitioners, amalgam manufacturers/distributors or regulatory agencies in Canada or elsewhere.

With regard to the epidemiological literature, there have been no adequately conducted epidemiological studies of amalgam bearers, with proper controls and objectively measured signs and symptoms. The studies which have been reported (Ahlquist et al. 1988, 1993; Lavstedt and Sundberg 1989) fail to provide unequivocal evidence of absence of effects due largely to methodological weaknesses. Lack of adequate control groups, potential bias in subjectively reported symptoms, and failure to focus on disease states most likely to arise from amalgam or Hg exposure limit their value in the current assessment. The number of animal studies which have employed amalgam specifically, rather than Hg^0, methyl Hg, mercuric chloride, or some other form, is also limited.

Further assessment of the database pertaining directly to amalgam was considered to be of little value in advancing our understanding of the risks, or lack thereof, from amalgam. These data have been extensively reviewed by the Swedish National Board of Health (1994), which concluded that available studies of the effects of amalgam in humans and animals has not shown that mercury from amalgam has an adverse effect on health, with the exception of isolated cases of allergic reactions.

Instead, this present assessment focused on exposure and risks from Hg vapour. Inhalation of Hg vapour is considered the primary route of exposure to Hg from amalgam (WHO, 1991). A large body of literature pertaining to occupational exposure and epidemiology associated with Hg vapour is available upon which to assess amalgam's potential hazard (i.e., health effects) with respect to Hg vapour exposure. These occupational studies, combined with human and animal studies on the pharmacokinetics and effects of Hg vapour at the organism, organ, tissue, cellular and biochemical levels, provide an adequate basis for identifying the most likely hazard(s) to occur as a result of exposure to Hg from amalgam, and for estimating the level of Hg exposure that may be considered tolerable for the majority of the non-occupational population.

The aims of this report were the following:

1. to quantify, for the Canadian population, the exposure to Hg from amalgam fillings, as well as exposure from other non-occupational sources;

2. to assess the hazard posed by exposure to Hg vapour, estimating the level of exposure which should be tolerable for the majority of the population;

3. to quantify, as accurately as possible, the proportion of the Canadian population which may exceed the 'tolerable' level of exposure to Hg, due to amalgam fillings.

4. to estimate the number of filled teeth which will not result in exceeding the identified tolerable daily intake for Hg vapour.

This report focused as much as possible on Hg vapour exposure and health effects reported for humans, as a sizeable data base of human studies exists. Studies related to other forms of Hg or to other mammalian species, tissues, organs, or cell lines were only discussed as needed to further substantiate observed effects or trends, or if direct human data have not been reported.

For the purpose of this assessment, the term 'adequate safety' was defined as Hg exposure at or below the tolerable daily intake (TDI). Both estimated exposure and the TDI are derived in subsequent chapters. Health Canada routinely regulates or manages risks from non-carcinogenic chemical substances to the general population on this basis. This report does not include a risk-benefit analysis. Although dental amalgam may pose some Hg exposure and subsequent risk, the risks associated with alternate dental materials, or alternate or absent dental care have not been assessed for comparitive purposes. This task was beyond the scope of the present work. Also, this report does not examine or discuss the exposures to, or possible hazards of, silver, copper, tin, or any other component of amalgam dental restorations.

2.0 What is mercury?

Mercury (or quicksilver) is a dense silver-white metal which is liquid at room temperature and is characterized by low electrical resistivity, high surface tension, and high thermal conductivity (Andren and Nriagu 1979; Environment Canada 1981).

Hg is found in the environment, not as the liquid metal, but mainly in the form of amalgams and inorganic salts which have lower vapour pressures than elemental Hg (Andren and Nriagu 1979). The two properties which largely determine the environmental behaviour of Hg are the high vapour pressure of metallic Hg, and the relative insolubility of ionic and organic forms. The vapour pressure of Hg is highly dependent on temperature and the tendency of liquid Hg to form small droplets increases its rate of evaporation. Hg can exist in three stable oxidation states: elemental Hg (Hg^0/Hg(0)), mercurous ion (Hg_2^{2+}/Hg(I)), and mercuric ion (Hg^{2+}/Hg(II)). Hg (II) forms both inorganic and organic salts, such as chlorides and sulphates, and organoHg compounds. OrganoHg compounds are characterized by covalent bonding of Hg to one or two carbon atoms to form compounds of the type R-Hg-X and R-Hg-R', where R and R' represent the organic moiety, and X represents a halogen. The organic moiety may take the form of alkyl, phenyl and methoxyethyl radicals (WHO 1976). A subclass of short-chained alkylmercurials, which include monomethyl (CH_3Hg^+) and dimethyl Hg ($(CH_3)_2Hg$), are the predominant organic Hg compounds found in nature. DimethylHg is less stable and more volatile than monomethyl compounds (Environment Canada 1981).

3.0 What is dental amalgam?

Dental amalgam is a mixture of metals consisting of approximately 50% metallic Hg, by weight, mixed with an alloy containing varying amounts of silver (up to 70%), copper (up to 30%) and tin (up to 30%), among other potential components (Berry et al. 1994). Typically in Canada, amalgam is prepared and sold in sealed single use capsules, where the liquid Hg and alloy mixture are separate. Immediately prior to use, the Hg and alloy are mixed together with the aid of an amalgamator. The amalgam sets within 30 minutes of mixing and placement. Prior to setting, the material is a soft metallic paste which is installed into the prepared tooth surface (Horsted-Bindslev et al. 1991).

Most of the Hg-containing dental amalgam used in Canada is supplied by 5 manufactures (Dentsply, Kerr, S.D.I., Ivoclar and Hoechst). The combined total quantity of Hg sold in Canada in 1994 by these 5 companies, as a component of their various dental amalgam products, was 2129.5 kg (personal communications to G.M.Richardson, 1994, 1995).

4.0 Dental health status of Canadians

Improvements in the dental health of Canadians suggest that the rate of use of dental restorative materials may have decreased over recent decades, and should continue to decrease for the foreseeable future. Over the past few decades, DMFT score (the total number of decayed, missing and filled teeth) has declined in the North American population, although available statistics are limited and trends, particularly in adults are difficult to interpret (Graves and Stamm, 1985; USDHHS, 1987). This decline is attributed to improved dental care and to the fluoridation of municipal water supplies (Graves and Stamm, 1985; Ismail et al, 1990). 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).

Of greatest significance with respect to Hg exposure is the number of filled teeth (i.e. teeth potentially containing dental amalgam). As observed with DMFT score, the number of filled teeth has also generally declined in children and teens (Graves and Stamm, 1985; Johnston et al., 1986). Based on the most recently published statistics for 13 year olds (the only age group consistently reported), the average number of filled teeth was: 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 between 1970 and 1972 as part of the Nutrition Canada Survey (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. For those 13 year olds with at least

one filled tooth (n=203), the average number of filled teeth was 4.48 (Health Canada, unpublished).

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.

Data on the number of filled teeth in the Canadian population were collected as part of the Nutrition Canada Survey (1971-72). These unpublished data indicated a mean number of filled teeth for all surveyed adults aged 18 to 102 years (n=7339) of 3.60, whereas the average for those with one or more filled teeth (n=3207) was 8.23 filled teeth (Health Canada, unpublished data). NCS data on average number of filled teeth, by specified age groups, are presented in Table 4.1.

No recent cross-sectional data on the number of filled teeth in the Canadian population have been collected since 1971-72. However, assuming that all individuals participating in the Nutrition Canada Survey of 1970-72 had no new fillings installed over the following 23 years, these data may be used to provide a conservative estimate of the incidence of filled teeth in Canadian adults in 1995. This can be done by comparing the incidence of filled teeth in descrete age groups from the 1970-72 Nutrition Canada Survey data with the incidence of filled teeth in age groups 23 years younger. These younger age groups would now (in 1995) be 23 years older. Comparison of these age groups indicated that the average incidence of filled teeth in adults aged 30 years or more in 1995 may be as much as 54% greater in 1995 compared to 1970-72.

This increase in number of filled teeth in North American adults over the past 1 to 2 decades is likely attributable, in part, to generally better dental care (particulary dental restoration versus tooth extraction) in children and teens than in adults in the 1970s and early 1980s. A decrease in the incidence of edentulism over the period from 1971-74 to 1985-86 (USDHHS 1987) provide more teeth, on average, to contain fillings.

Table 4.1. Average number of filled teeth (± s.d.), by age group, for the Canadian population. Unpublished data collected between 1970 and 1972 as part of the Nutrition Canada Survey. Age groups after HC (1994).

Age group	All individuals surveyed (n)	Individuals with ; 1 filled tooth (n)	Percent of sample with filled teeth
toddler [a] (3-4 yr)	0.17 ± 0.85 (n=543)	3.36 ± 1.87 (n=28)	5.2
child (5-11 yr)	1.69 ± 2.70 (n=2083)	4.18 ± 2.76 (n=841)	40.4
teen (12-19 yr)	3.59 ± 4.37 (n=2316)	6.06 ± 4.16 (1373)	59.3
adult (20-59 yr)	4.57 ± 5.95 (N=4788)	8.65 ± 5.64 (N=2529)	53.8
senior [b] (60+ yr)	1.25 ± 3.35 (N=2209)	6.12 ± 5.00 (N=451)	20.4

a this age group normally comprises individuals aged 1.5 to 4 years (HC, 1994), however, no individuals less than 3 years of age were reported with filled teeth.

b HC (1994) includes seniors in the adult age group (20+ years).

5.0 Mercury Exposure

Hg exposure does occur from amalgam dental fillings, and this exposure increases as the number of fillings increases. Concentrations of Hg in urine, a biomarker of inhalation exposure (and, to a lesser extent, other sources of exposure) (WHO, 1991), are higher in individuals with amalgam fillings than in those without, and correlate positively with number of filled teeth, number of filled tooth surfaces, number of filled occlusal surfaces, total amalgam surface area, or other indices of amalgam load (Aronsson et al. 1989; Akesson et al. 1991; Skerfving 1991; Langworth et al. 1991; Jokstad et al. 1992; Svensson et al. 1992; Suzuki et al. 1993; Herrmann and Schweinsberg 1993; Schweinsberg 1994; Skare and Engqvist 1994). Hg levels in other tissues also increase with increasing amalgam load, including blood (particularly blood plasma) (Abraham et al. 1984; Snapp et al. 1989; Molin et al. 1990; Akesson et al. 1991; Jokstad et al. 1992; Svensson et al. 1992; Herrstrom et al. 1994), kidney (Nylander et al. 1987), brain (Friberg et al. 1986; Nylander et al. 1987; Eggleston and Nylander 1987; Weiner and Nylander 1993), pituitary gland (Nylander et al. 1989; Weiner and Nylander 1993), abdominal muscle (Weiner and Nylander 1993) and oral mucosa (Willershausen-Zonnchen et al. 1992). Urine and blood Hg levels decline after amalgam removal (Snapp et al. 1989; Molin et al. 1990; Skerfving, 1991). The amount of Hg excreted as a result of chelation therapy increased as the number of amalgam fillings increased (Aposhian et al. 1992; Herrmann and Schweinsberg 1993), with about two thirds of the body burden of excretable Hg associated with exposure arising from amalgam fillings (Aposhian et al. 1992).

Exposure to Hg from amalgam fillings appears to be predominantly via inhalation of elemental Hg (Hg^0) (WHO 1991). Hg is released from amalgam fillings as Hg^0, and is routinely detected in exhaled or intra-oral air (Gay et al. 1979; Svare et al., 1981; Patterson et al. 1985; Vimy and Lorscheider, 1985a; Berglund et al. 1988; Jokstad et al. 1992), at concentrations which increase with the number of filled teeth (Svare et al. 1981; Vimy and Lorscheider 1985a; Patterson et al. 1985; Jokstad et al. 1992). *In vitro* data suggest the rate of release of Hg^0 from a single amalgam filling may be as high a 15 µg Hg/day (Gross and Harrison 1989). *In vivo* measurements, however, suggest release rates ranging from 0.6 to 2.5 µg Hg/filling/day (derived from the data of Vimy and Lorscheider 1985a; Aronsson et al. 1989; Berglund 1990; Skare and Engqvist 1994). Release of Hg^0 from occlusal surfaces, *in vivo*, increases with the intensity and duration of stimulation such as chewing or brushing (Svare et al. 1981; Vimy and Lorscheider 1985a,b; Berglund 1990), and with temperature, such as might be increased by consumption of hot beverages (Fredin 1994). Oral breathing results in inhalation of this vapour, however dilution occurs with inflowing fresh air (Langworth et al. 1988). In the lungs, Hg absorption in the range of 60 to 100% has been reported (Neilsen-Kudsk 1965; Hursh et al. 1976; Teisinger and Fiserova-Bergerova, 1965; Oikawa et al. 1982).

Aside from Hg vapour released into the oral cavity, amalgam particles, Hg^0 and/or Hg^{2+} may also be suspended or dissolved in saliva (reviewed by Marek 1992). Hg has been found dissolved, *in vitro*, in distilled water (Kuc et al. 1981), in saline solution (Kozono et al.

1982; Okabe et al. 1987) and natural saliva (Brune and Evje, 1985; Uusheimo and Rytomaa 1988) in which amalgam was immersed or coated. Collection of samples followed simulated brushing or other stress in some experiments. Hg has also been measured in saliva *in vivo*, in association with amalgam fillings (Kuc et al. 1981; Berglund 1990). Particles of amalgam material are also released into the oral cavity (Uusheimo and Rytomaa 1988; Marek 1992) due to corrosion (Brune and Evje 1985; Eley and Cox 1993) or abrasive stress (particularly in individuals suffering bruxism) (Sallsten et al. 1991; Marek 1992). Dental plaque from amalgam surfaces has significantly greater Hg contamination than plaque from enamel surfaces of amalgam bearers, while plaque from patients with no amalgam fillings has no detectable Hg (Lyttle and Bowden 1993).

Gastrointestinal absorption of inorganic Hg is lower than via the lung (WHO 1991). Absorption of Hg from the ingestion of abraded particles should be low, as gastrointestinal absorption of metallic Hg is likely less than 1% (Elinder et al. 1988). Assuming that Hg^0 dissolved in saliva is oxidized to Hg^{2+} (USDHHS, 1993), gastrointestinal absorption would still be much lower than via the lung, as Hg^{2+} absorption from the gut is probably less than 10% (Elinder et al. 1988).

It is postulated that inorganic Hg from amalgam may be methylated in the gastrointestinal tract, resulting in greater absorption from the gut. The methylation of Hg by oral bacteria (Heintze et al. 1983) and intestinal microflora (Rowland et al. 1975) have been demonstrated *in vitro*. However, despite the near complete absorption of methyl Hg in the gastrointestinal tract (WHO 1990), it is unclear what, if any, significant contribution this potential biotransformation might make to Hg exposure in persons with amalgam fillings. A significant, positive association between amalgam load and erythrocyte Hg (the primary site of methyl Hg transport in blood (WHO 1990)) levels would be expected if this pathway of exposure was significant. Results, however, are mixed. Svensson et al. (1992) and Langworth et al. (1991) reported significant positive associations between amalgam load and plasma Hg levels (plasma is the primary site for transport of Hg^{2+}) but not between amalgam load and Hg levels in whole blood and/or erythrocytes. Akesson et al. (1991) and Molin et al. (1990) reported significant positive associations between amalgam load and both plasma and erythrocyte Hg levels, although the latter associations were much weaker. This pathway is not considered further in this analysis, for lack of unequivocal data demonstrating it to be significant compared to inhalation of Hg vapour.

Other postulated routes of exposure include absorption by oral mucosa, migration through root canals and into tooth pulp and the jaw, and possible direct transfer to the brain from nasal sinuses (WHO 1991). However, data are very limited or non-existent which demonstrate that these routes exist and might be significant. Therefore, these will not be further discussed in this report.

The human fetus is exposed to Hg originating from maternal amalgam fillings. A recent study (Drasch et al. 1994) found statistically significant positive associations between the number of amalgam fillings in the mother and the levels of Hg in: a) fetal liver; b) fetal

renal cortex; c) the renal cortex of older infants (11-50 weeks old); d) the cerebral cortex of older infants. Levels of Hg in fetal brain tissue were not reported. Some observations of Drasch et al. (1994), suggest that Hg originating from maternal amalgam may not be deposited in fetal CNS tissue *in utero*. The association between maternal amalgam status and Hg in the cerebral cortex of deceased newborns (aged 0 to 10 weeks) was not statistically significant, and the mean Hg concentration in cerebral cortex tissue of older infants (aged 11 to 50 weeks) of mothers with 0 to 2 filled teeth was not statistically different from that of older infants of mothers with more than 10 filled teeth. No abnormal histopathological signs or lesions were observed in any of the tissues sampled (Dr. A. Hildebrandt, Bundesinstitut fur Arzneimittel und Medizinprodukte, Germany, personal communication, 1994).

Transfer of Hg from maternal amalgam to the fetus has also been observed in sheep (Vimy et al. 1990) implanted with amalgam fillings. Likewise, transfer of Hg to the fetuses of guinea pigs (Yoshida et al. 1986, 1990), rats (Clarkson et al. 1972) and mice (Khayat and Dencker 1982) results from exposure of pregnant female animals to Hg vapour.

It is unclear to what extent, if any, Hg originating from amalgam fillings is passed to infants via breast feeding. Klemann et al. (1990) found no correlation between maternal dental amalgam status and Hg levels in breast milk. However, that study failed to control for fish consumption or other factors that would confound the association between breast milk Hg levels and amalgam status. No other published human studies examining this issue were located. The study of Drasch et al. (1994) failed to control their statistical analysis for breast feeding in neonates, infants and children. Therefore, that study does not permit any indirect assessment of the possible role of breast milk contamination in neonate, infant or child exposure. Animal models have demonstrated the transfer of Hg to breast milk following exposure of guinea pigs to Hg vapour (Yoshida et al. 1992) and after i.p. injection with $HgCl_2$ (Yoshida et al. 1994). Hg arising specifically from dental amalgam was detected in the milk of sheep (Vimy et al. 1990).

5.1 Quantification of Hg Exposure

The Hg exposure arising from amalgam has never been quantified for the Canadian population as a whole. Richardson et al. (1995) estimated that 7 filled teeth may give rise to an absorbed dose of approximately 2.25 µg Hg/adult/day and that this amounted to 42% of total absorbed Hg daily dose for the 'average' Canadian adult. Estimates for other age groups were also reported. Various other authors have attempted to estimate Hg exposure arising from amalgam fillings, with estimates ranging from 1.24 µg Hg/person/day to 27 µg Hg/person/day, relating varyingly to individuals with ;14 amalgam fillings, ,4 amalgams or 1 to 16 amalgams, etc. (summarized by Vimy and Lorscheider, 1990 and WHO, 1991). Using direct metabolic studies, Skare and Engqvist (1994) reported that a group of 9 volunteers with an average of about 47 amalgam-filled tooth surfaces had a daily exposure of 12 µg Hg/day, and Aposhian et al. (1992) reported 66% of human body burden of Hg was derived from amalgam.

For the present assessment, probabilistic methods (Burmaster and von Stackelberg 1991; Thompson et al. 1992) were used to estimate exposure of the Canadian population to Hg arising from dental amalgam and other sources. It is recognized that individuals differ in the number of fillings they possess. Also, the variables required to estimate exposure (such as the number of filled teeth, Hg release rate from fillings, breathing patterns and rates, Hg absorption rates, etc.) are not precisely known or vary from individual to individual. These variations and uncertainties in input variables introduce variance and uncertainty into the estimates of Hg exposure. Standard deterministic methods, which employ single point estimates of input variables, fail to recognize or quantify the variance or uncertainty in exposure estimates across a population. Also, use of worst case point estimates rather than average or typical values for input variables can result in over-estimation of exposure. Finally, probabilistic methods, employing the known, reported or best estimate of the range of values of input variables (represented as probability density functions), combined with alternate values where uncertainty in the data is large, can provide an estimate of exposure for which some statistical likelihood can be assigned.

A variety of theories and assumptions have been postulated as a basis to estimate exposure to Hg from amalgam. One aspect of debate is whether or not ingestion of Hg dissolved or suspended in saliva is a significant source of exposure, along with inhalation of Hg vapour arising from amalgam. In order to quantify Canadian population exposure, two different probabilistic exposure assessments were undertaken. The first method was based on the general approach of Olsson and Bergman (1992), in which ingestion of Hg in saliva was considered. Probability density functions for all parameters were employed to estimate exposure to Hg evolving from amalgam-filled tooth surfaces.

The second approach followed that of Richardson et al. (1995), where only inhalation exposure was considered. This latter analysis employed empirical associations reported between the number of amalgam-filled teeth and urine Hg levels (after Skerfving, 1991), and between urine Hg levels and exposure to Hg vapour (after Roels et al. 1987). It also incorporated the inter-individual variation in these reported empirical associations to produce probability density functions of estimated exposure to amalgam. Probabilistic estimates of exposure arising from other non-occupational sources of exposure, including indoor and outdoor air, drinking water, food, soil and dust were also incorporated in this latter analysis. From this, the relative contribution of dental amalgam to total Hg exposure for the Canadian population was deduced.

5.2 Exposure Assessment I - after Olsson and Bergman (1992)

Equations used for estimating exposure are based on those published by Olsson and Bergman (1992). In this assessment, Excel™ version 4.0 (Microsoft Corp., 1992) and Crystal Ball™ version 3.0 (Decisioneering Inc., 1993) were used to perform the dose calculations.

Mercury doses from amalgam were deemed to comprise two parts: an inhaled dose and an ingested dose. According to Olsson and Bergman (1992) the amount of Hg vapour inhaled by an individual with amalgam fillings (expressed in g/day) can be estimated as:

$$\text{Dose} = \sum_{i=1}^{m} R_i \bullet t_i \bullet F_i \bullet IR \bullet A_{inh}$$

where:

m = the number of activities during which exposure occurs;
R_i = the rate of Hg release in g/hour during activity i;
t_i = the number of hours per day spent at activity i;
F_i = the oral breathing ratio (expressed as a fraction of the total) during time t_i ;
IR = the inspiration to expiration ratio;
A_{inh} = the inhalation absorption factor.

Similarly, the amount of Hg ingested with saliva (expressed in g/day) can be estimated as:

$$\text{Dose} = \sum_{i=1}^{m} R_i \bullet t_i \bullet (1 - F_i) \bullet A_{ing}$$

where:

A_{ing} = the ingestion absorption factor, and the other variables are as defined above.

The total daily dose of Hg from amalgam is defined as the sum of the inspired and ingested doses.

It should be noted that the method of Olsson and Bergman (1992) is independent of the rate of breathing and the rate of saliva ingestion. For a simple illustration of this independence, one might consider two people whose amalgam fillings emit the same amount of Hg per unit time and who have the same oral breathing ratio, but one of whom breathes faster and has a higher respiratory volume than the other. The Olsson and Bergman (1992) model determines that both these people are exposed to the same amount of Hg vapour. This is rational because the Hg builds to a higher concentration in the mouth of the slower, shallower breather. The same analogy can be used to explain the independence of the dose calculations with the rate of saliva
production and ingestion.

In this assessment, baseline Hg release rates were estimated for each age group and were used to calculate estimated doses during sleep and during activities not deemed to stimulate amalgam. Mercury release rates during amalgam-stimulating activities (eating and tooth brushing) were estimated by multiplying the baseline release rate by a stimulation magnification factor. The equations used to calculate the baseline and stimulated Hg release rates are as follows:

$$R_b = n_f \bullet n_s \bullet R$$

and

$$R_s = R_b \bullet F_{sm}$$

where:

R_b = the baseline Hg release rate in g/day;
n_f = the number of filled teeth;
n_s = the number of amalgam surfaces per filled tooth;
R = the rate of Hg release in g/day per amalgam surface;
R_s =the stimulated Hg release rate in g/day; and
F_{sm} = the stimulation magnification factor.

Inhaled doses delivered and absorbed while sleeping were calculated as:

$$D_{inh,s} = R_b(t_s/24) \bullet Fs \bullet 0.5 \bullet A_{inh}$$

where:

$D_{inh,s}$ = the Hg dose from sleeping in g/day;
t_s = the time spent sleeping in hr/day;
F_s = the oral breathing ratio while sleeping;
0.5 = the inspiration to expiration ratio;
A_{inh} = the inhalation absorption factor;

and R_b is as defined above.

Doses from amalgam-stimulating activities (eating and tooth brushing) were calculated in two parts: the dose delivered during the actual activity and the dose delivered during the passivation period immediately following the activity. During the passivation period, the Hg release rate was assumed to decay exponentially from R_s to R_b. The inhaled dose from eating was thus calculated as:

$$D_{inh,m} = R_s(t_m/1440) \bullet F_a \bullet 0.5 \bullet A_{inh} + n_m((T_p/1440)(R_b - R_s)/ln(R_b/R_s)) \bullet F_a \bullet 0.5 \bullet A_{inh}$$

where:

$D_{inh,m}$ = the Hg dose from eating in g/day;
t_m = the time spent eating in min/day;
F_a = the oral breathing ratio while awake;
n_m = the number of meals and/or snacks per day (a whole number);
T_p = the passivation period in minutes;

and the other factors are as defined above.

The dose from tooth brushing was similarly calculated as:

$$D_{inh,t} = R_s(t_t/1440) \bullet F_a \bullet 0.5 \bullet A_{inh} + n \bullet ((T_p/1440)(R_b - R_s)/ln(R_b/R_s)) \bullet F_a \bullet 0.5 \bullet A_{inh}$$

where:

$D_{inh,t}$ = the Hg dose from tooth brushing in g/day;
t_t = the time spent tooth brushing in min/day;

n_t = the number of tooth brushings per day (a whole number);
and the other factors are as defined above.

The inhaled dose from activities other than sleeping, eating and tooth brushing was estimated by calculating the time unaccounted for by these three activities and applying the baseline Hg release rate. The equation is as follows:

$$D_{inh,o} = R_b(1440 - 60 \bullet t_s - t_m - t_t - (n_m+n_t)T_p)/1440 \bullet F_a \bullet 0.5 \bullet A_{inh}$$

where:

$D_{inh,o}$ = the Hg dose from other activities in g/day;
and the other factors are as defined above.

Ingested Hg doses were calculated in a manner similar to that used for calculating inhaled doses. The ingested dose delivered and absorbed while sleeping was calculated as:

$$D_{ing,s} = R_b(t_s/24) \bullet (1 - F_s) \bullet A_{ing}$$

where:

$D_{ing,s}$ = the Hg dose from sleeping in g/day
A_{ing} = the ingestion absorption factor,
and the other factors are as defined above.

The ingested doses from eating ($D_{ing,m}$), tooth brushing ($D_{ing,t}$) and other activities ($D_{ing,o}$) were calculated as follows:

$$D_{ing,m} = R_s(t_m/1440) \bullet (1 - F_a) \bullet A_{ing} + n_m((T_p/1440)(R_b - R_s)/ln(R_b/R_s)) \bullet (1 - F_a) \bullet A_{ing}$$

$$D_{ing,t} = R_s(t_t/1440) \bullet (1 - F_a) \bullet A_{ing} + n_t((T_p/1440)(R_b - R_s)/ln(R_b/R_s)) \bullet (1 - F_a) \bullet A_{ing}$$

$$D_{ing,o} = R_b \bullet (1440 - 60 \bullet t_s - t_m - t_t - (n_m+n_t)T_p)/1440 \bullet (1 - F_a) \bullet A_{ing}$$

5.2.1 Selection of input variables

Probability density functions were used to represent input variables for which more than one value was possible. The characterization of each parameter's probability density function is described below. The rationale for selecting each probability density distribution is also discussed in the text.

5.2.2 Release rate per amalgam-filled surface

Skare and Engqvist (1994) provide the most recent and extensively documented *in vivo* data on release rate per filled tooth surface. They used two different methods to measure the rate of Hg release into the mouths of 42 adult subjects and correlated the rate of release with the number of amalgam surfaces. The figure from their paper that illustrated this correlation is reproduced here as Figure 5.1. For the purposes of this study the release rate was modelled with a normal distribution with a mean value of 0.73 µg/day-surface (Skare and Engqvist's regression line slope, indicated on Figure 5.1). For the standard deviation, a value of 0.3 µg/day-surface was assumed, as approximately two-thirds of the data points on Figure 5.1 lie between lines with slopes (0.73 - 0.3) µg/day-surface and (0.73 + 0.3) µg/day-surface.

5.2.3 Stimulation magnification factor

Several researchers have shown that Hg concentrations in intra-oral air increase several times upon stimulation by chewing, eating or tooth brushing. Figure 5.2 summarizes average degrees of magnification determined by selected authors. The weighted average stimulation magnification factor was 5.3, from the data shown on Figure 5.2.

Data for individual subjects provided by Gay et al. (1979), Svare et al. (1981) and Berglund (1990) suggest a probable frequency distribution, illustrated on Figure 5.3. Since this distribution appears skewed, with most data in the 1 to 5 range, a log-normal distribution with a mean of 5.3 and a standard deviation of 4.3 was assumed in the assessment in order to approximate the shape of the distribution on Figure 5.3. This log-normal distribution is superimposed on Figure 5.3 for comparison.

Figure 5.1 Oral Hg release rate versus number of filled tooth surfaces (from Skare and Enqvist, 1994)

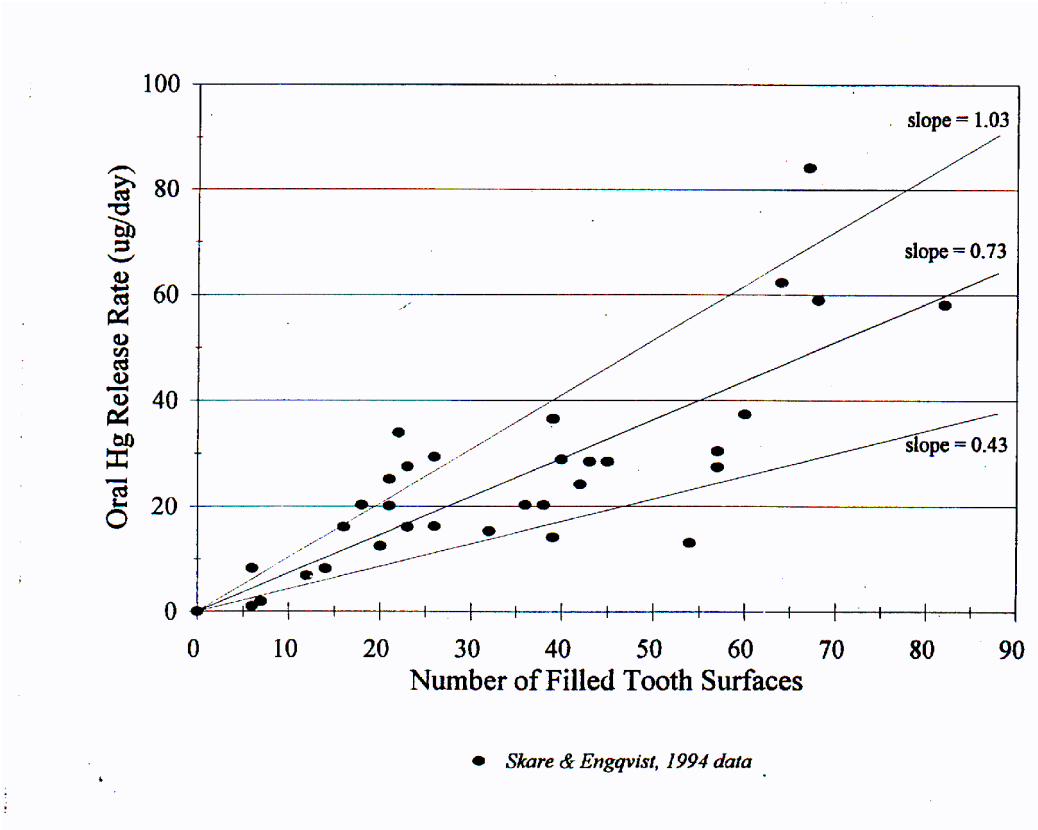


Figure 5.2 Comparison of reported average stimulation magnification factors.

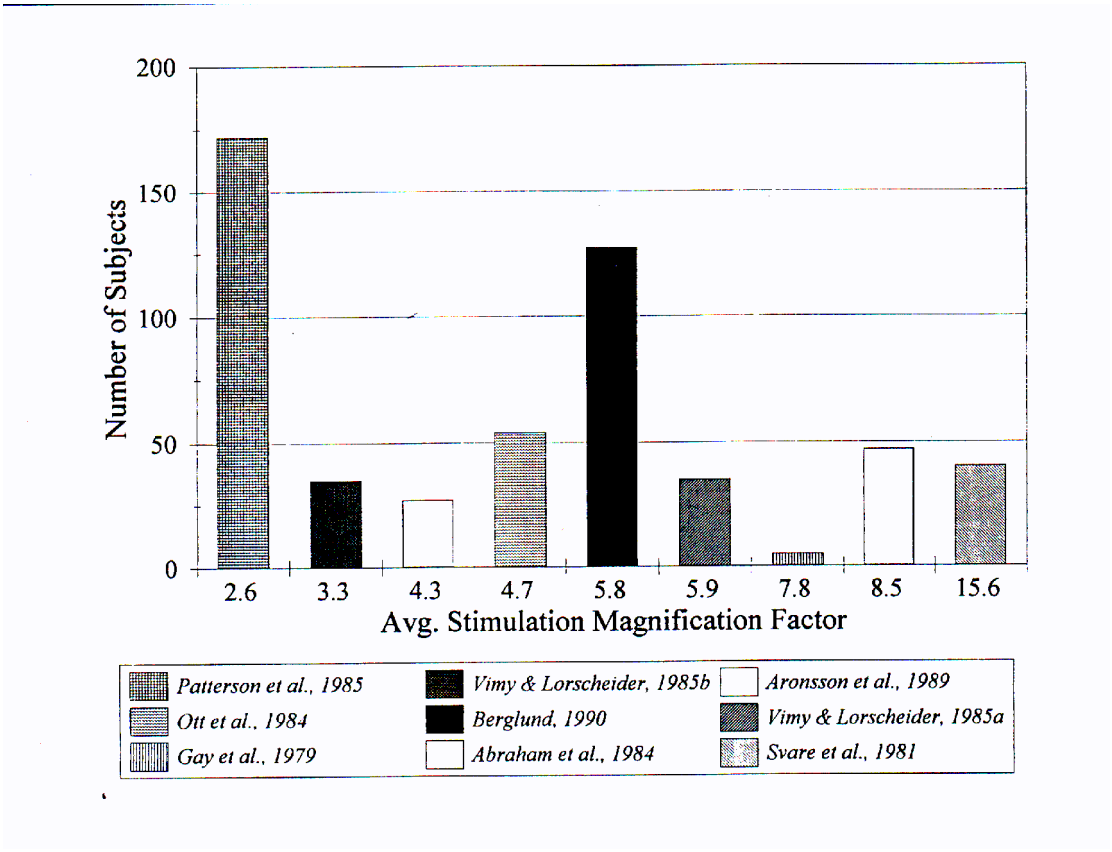
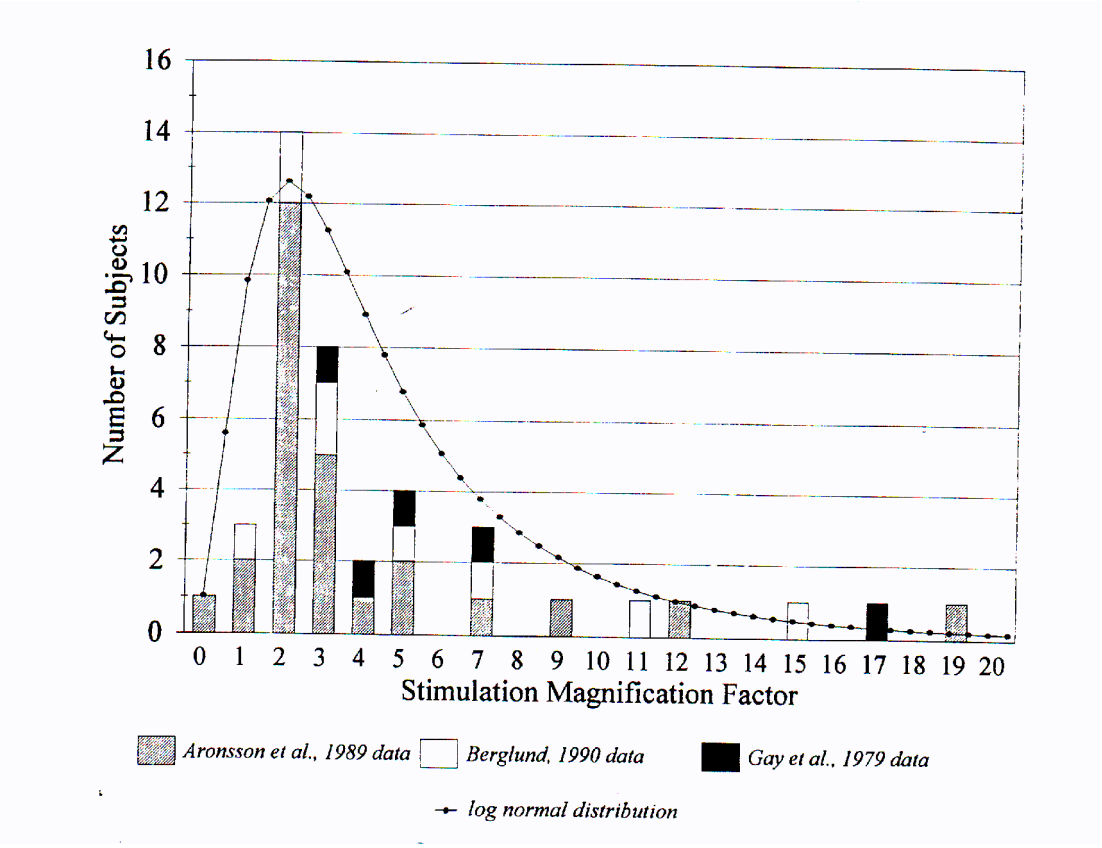


Figure 5.3. Probability density function of the stimulation magnification factor.



5.2.4 Lasting effect of stimulation

Vimy and Lorscheider (1985b) measured changes in Hg concentrations in intra-oral air during and after gum chewing. Including the time spent chewing, concentrations remained significantly elevated above baseline levels for at least 60 minutes and possibly beyond 120 minutes. Hg emission remained at its maximum throughout the period of stimulation. Once gum chewing ceased, the Hg emission rate declined gradually (approximately exponentially) over the next 60 minutes and more. This decay function has been defined in the equation for $D_{inh,m}$, above.

For the purposes of this study it was assumed that each chewing or tooth brushing activity results in maximally elevated Hg emissions for the duration of that activity (defined in section 5.2.9). Reduction in Hg emission was then assumed to follow exponential decay for 60 to 120 minutes following cessation of stimulation. Any duration for this passivation period, between 60 and 120 minutes, was considered equally likely.

5.2.5 Inhalation absorption factor

Most of the published estimates for Hg exposure have assumed an inhalation absorption factor of 80%. Measurements of Hg vapour absorbed in the lungs reported by Teisinger and Fiserova-Bergerova (1965) and Neilsen-Kudsk (1965) ranged from 74% to 79% and from 67% to 86%, respectively. A later study using radioactive Hg vapour indicated absorption was in the range of 61% to 82% (Hursh et al., 1976). Less than 100% absorption is expected since not all Hg in inhaled air would contact lung surfaces prior to being exhaled. Data for five subjects suggest that absorption is greater in slower breathers (Hursh et al., 1976), as would be expected when greater time is permitted for inhaled Hg to contact lung surfaces for absorption.

For the purposes of this study it was assumed that the inhalation absorption factor is uniformly distributed between 61% and 86%, i.e., any value in this range is equally likely. Data were insufficient to define any other shape of the probability density function. Although slower breathing appears to result in greater absorption (Hursh et al., 1976), data were insufficient to assess the impact of this on exposure estimates. There do not appear to be any published data relating to absorption by children, and thus it was assumed that all age groups absorb Hg vapour at the same rate.

5.2.6 Ingestion absorption factor

Hg vapour that becomes dissolved in saliva and swallowed may be expected to become almost completely oxidized to inorganic Hg (Hg^{2+}) (USDHHS, 1993). Ingestion absorption factors for inorganic Hg (Hg^{2+}) have been reported to be in the range of 5 to 10% (WHO 1991), but up to 15% of mercuric nitrate was absorbed by human volunteers (Rahola et al. 1973). For the purposes of this study it was assumed that all Hg swallowed becomes oxidized to Hg^{2+} ions and that it is absorbed at a rate uniformly distributed between 5% and 15%.

5.2.7 Number of filled teeth

Unpublished data from the Nutrition Canada Survey (1970-1972) describe the number of fillings in the mouths of 11,957 Canadians (see Table 4.1). These data were presented separately for each age group being considered so they were used directly to produce discrete probability distributions for each age group, shown on Figures 5.4 to 5.8, inclusive. Note that in this assessment, exposure and risks were calculated only for the fraction of the population having filled teeth, and not for the Canadian population as a whole.

Although these data were collected between 1970 and 1972, they were considered reasonably representative of current Canadian occurrence of filled teeth in the population. Data for the number of filled teeth for 13 year olds was in reasonable agreement with various provincial data from 1980 to 1985, and the number of filled teeth in adults agrees well with the incidence of filled teeth in the U.S. in 1985-86, the most recent statistics for that country (see Section 4.0).

Although some data suggest that the number of filled teeth in toddlers, children and teens may have declined by 30 to 50% since the early 1970s, data also suggest that the number of filled teeth in adults and seniors may have increased by this same amount (discussed in section 4.0). As no recent (post-1972) cross-sectional population data exist on the number of filled teeth for the Canadian population, the NCS data were assumed to be representative.

5.2.8 Number of surfaces per filling

Since the Hg release rate used in this assessment was defined as a function of the number of amalgam surfaces rather than the number of filled teeth, the Nutrition Canada Survey data for the number of filled teeth could not be used directly. A study of cadavers conducted by Nylander et al. (1987) reported both the number of amalgam fillings and the number of amalgam surfaces per filled tooth for 25 subjects. In the absence of any data more directly applicable to Canadians of all ages, these data were used to estimate the numbers of amalgam surfaces. Figure 5.9 shows the frequency distribution for the average number of filled surfaces per filled tooth for the 25 subjects in the Nylander et al. (1987) study. In this assessment, a log-normal distribution with a minimum of 1, maximum of 5, mean of 1.65, and standard deviation of 0.62 surfaces/filled tooth was assumed. This probability distribution is superimposed on Figure 5.9 for comparison.

5.2.9 Eating habits

It has been demonstrated that the mechanical action of chewing on filled teeth causes temporary increases in the emission of Hg vapour from dental amalgam and that the elevated levels gradually decline after eating stops (Vimy and Lorscheider, 1985b).

Time-activity data, for exposure assessment purposes, have been collected in recent years by the California Environmental Protection Agency Air Resources Board (Wiley et al., 1991a,b). These data include mean values for total time spent eating. For the purposes of this assessment, log-normal probability density distributions were used to represent the total

amount of time spent eating by members of each age group. For toddlers and children, the averages cited in Wiley et al. (1991a) for 3 to 5 year-olds and 6 to 11 year-olds, respectively, were used as mean values for the log-normal distributions. Similarly, for teenagers, adults and seniors, the averages cited in Wiley et al. (1991b) for 12 to 17 year-olds, 18 to 64 year-olds, and persons 55 years and older, respectively, were used as mean values. The coefficient of variation for adults cited in Wiley et al. (1991b), 0.78, was used to define standard deviations for all age groups. The parameters used for

Figure 5.4. Occurrence of filled teeth in toddlers (aged 3 and 4 years; from Nutrition Canada Survey, unpublished data). N = 28 out of a total of 544 toddlers surveyed.

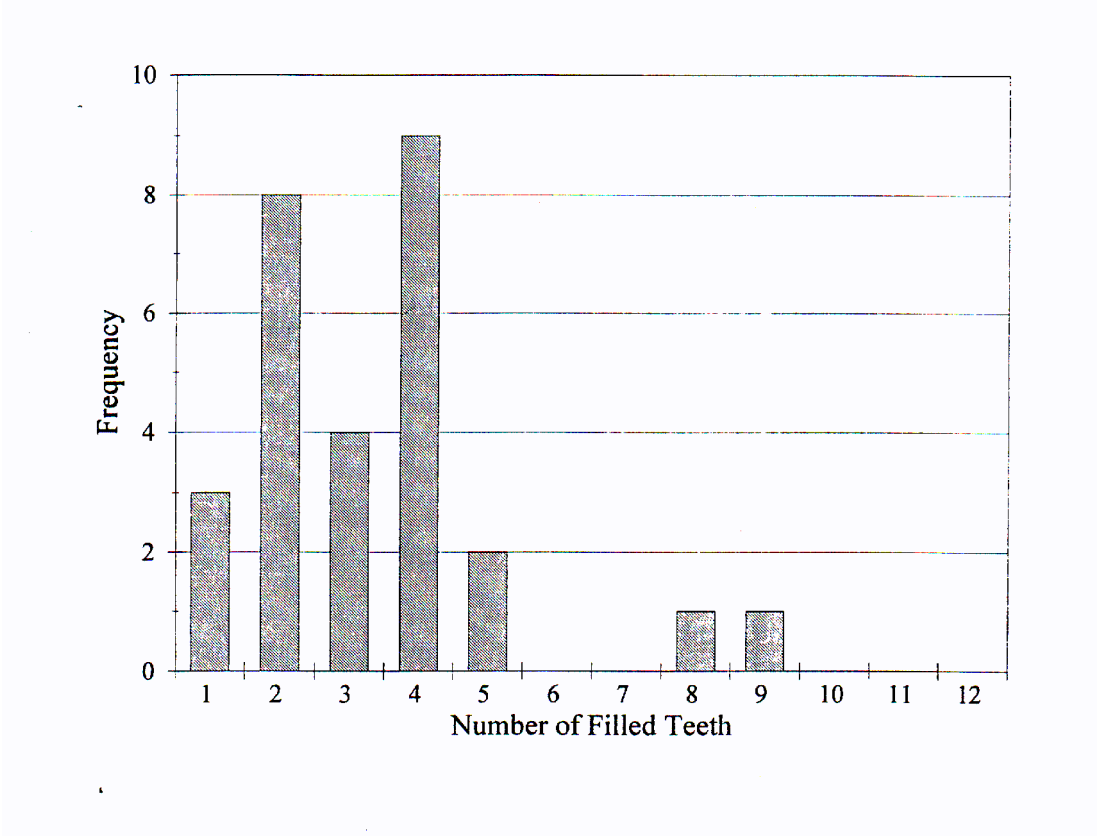


Figure 5.5. Occurrence of filled teeth in children (aged 5 to 11 years; from Nutrition Canada Survey, unpublished data). N = 842 out of 2,084 children surveyed.

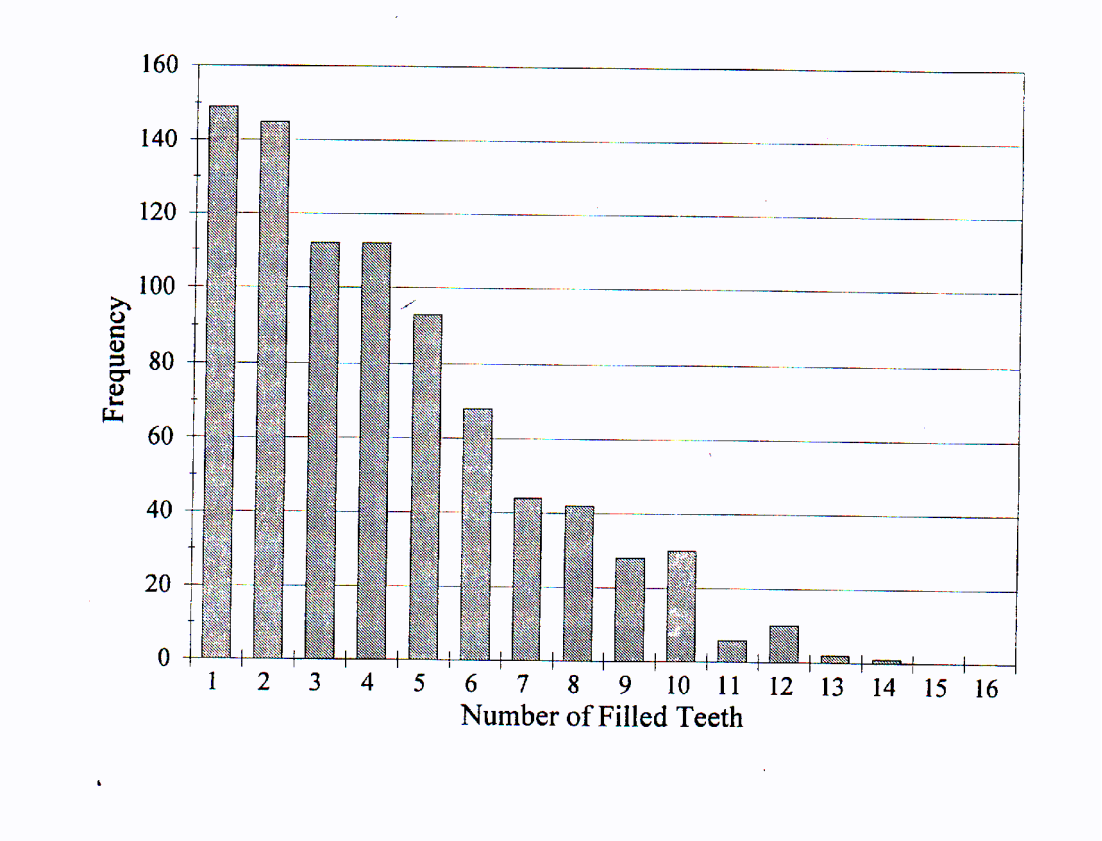


Figure 5.6. Occurrence of filled teeth in teens (aged 12 to 19 years; from Nutrition Canada Survey, unpublished data). N = 1373 out of 2316 teens surveyed.

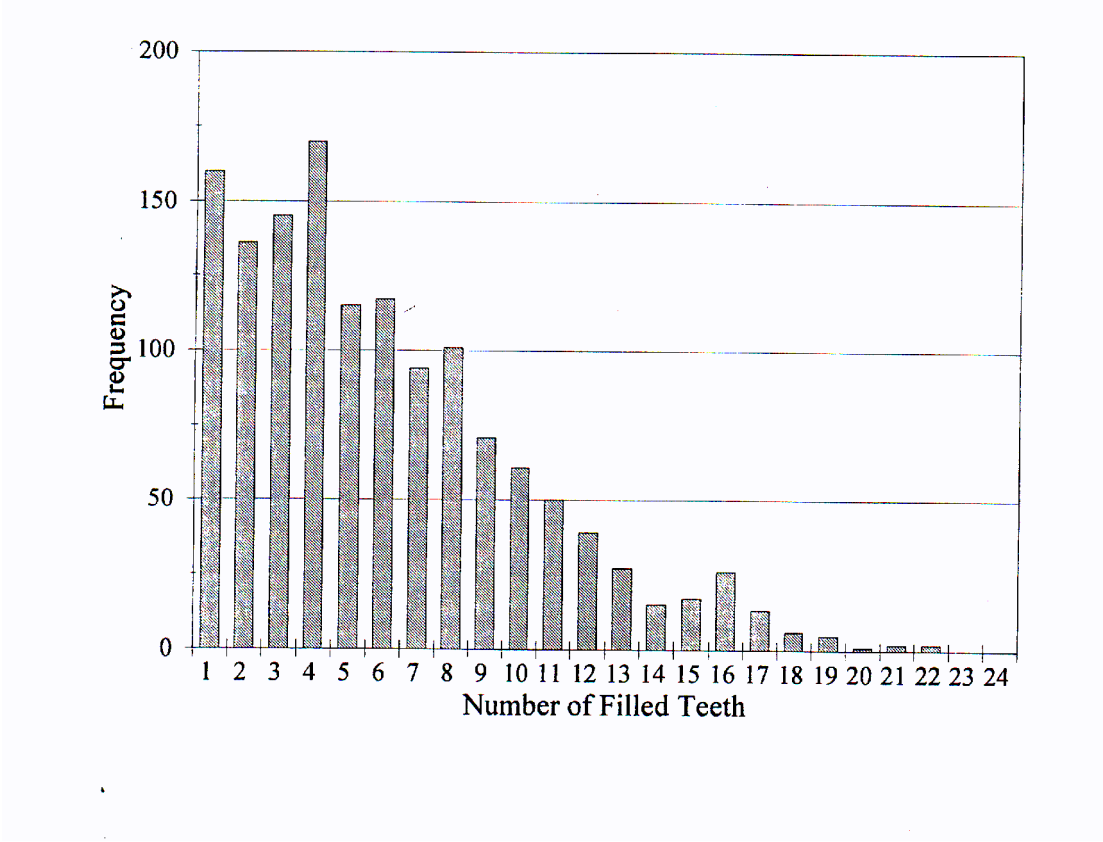


Figure 5.7. Occurrence of filled teeth in adults (aged 20 to 59 years; from Nutrition Canada Survey, unpublished data). N = 2533 out of 4801 adults surveyed.

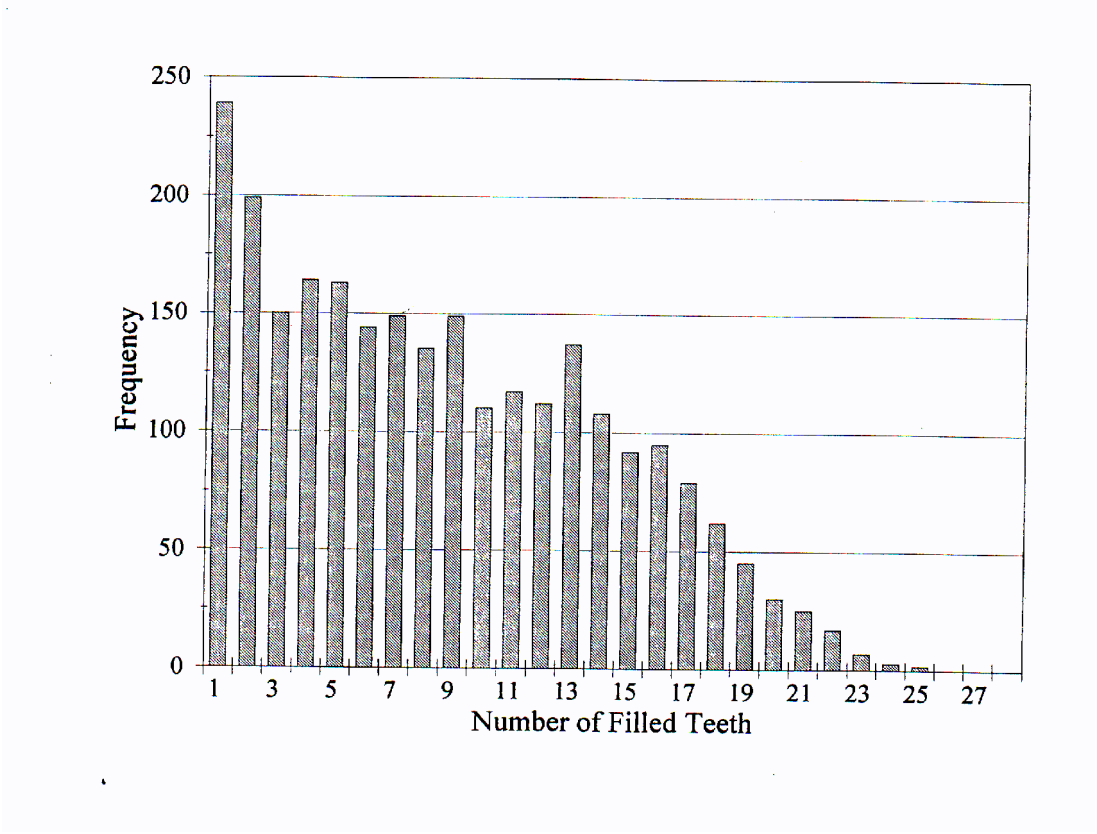


Figure 5.8. Occurrence of filled teeth in seniors (aged 60+ years; from Nutrition Canada Survey, unpublished data). N = 451 out of 2212 seniors surveyed.

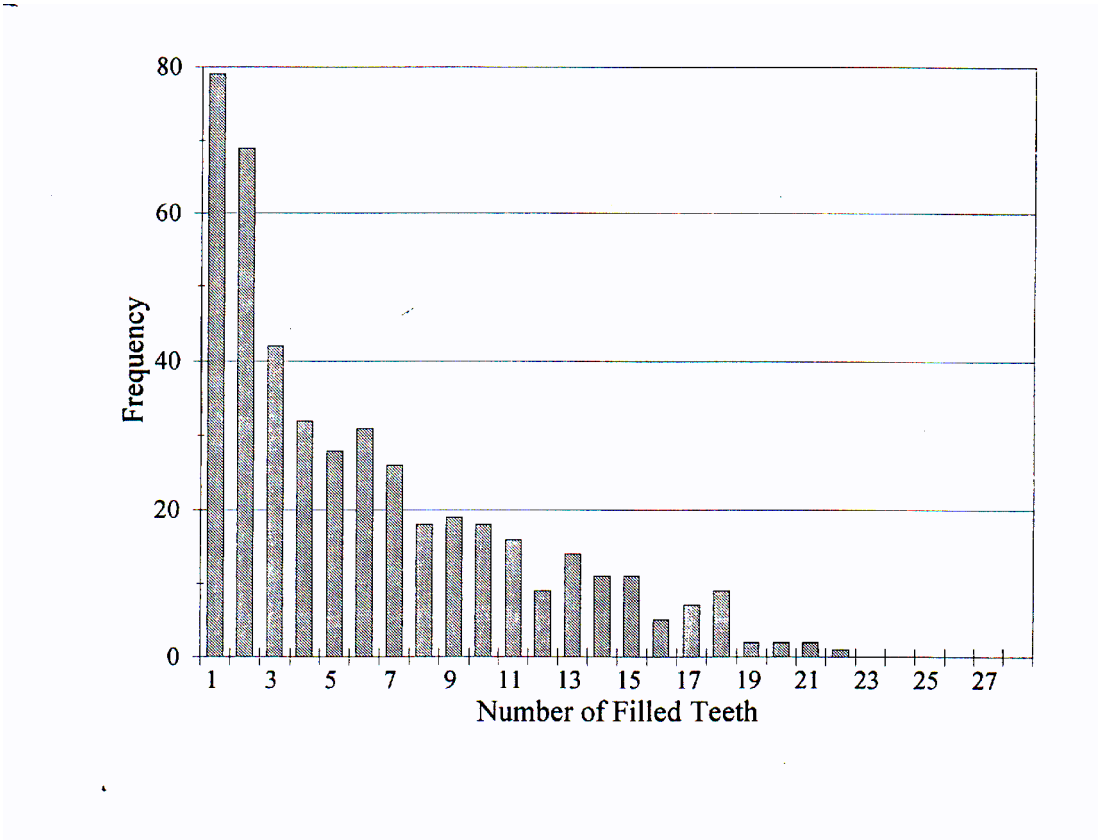
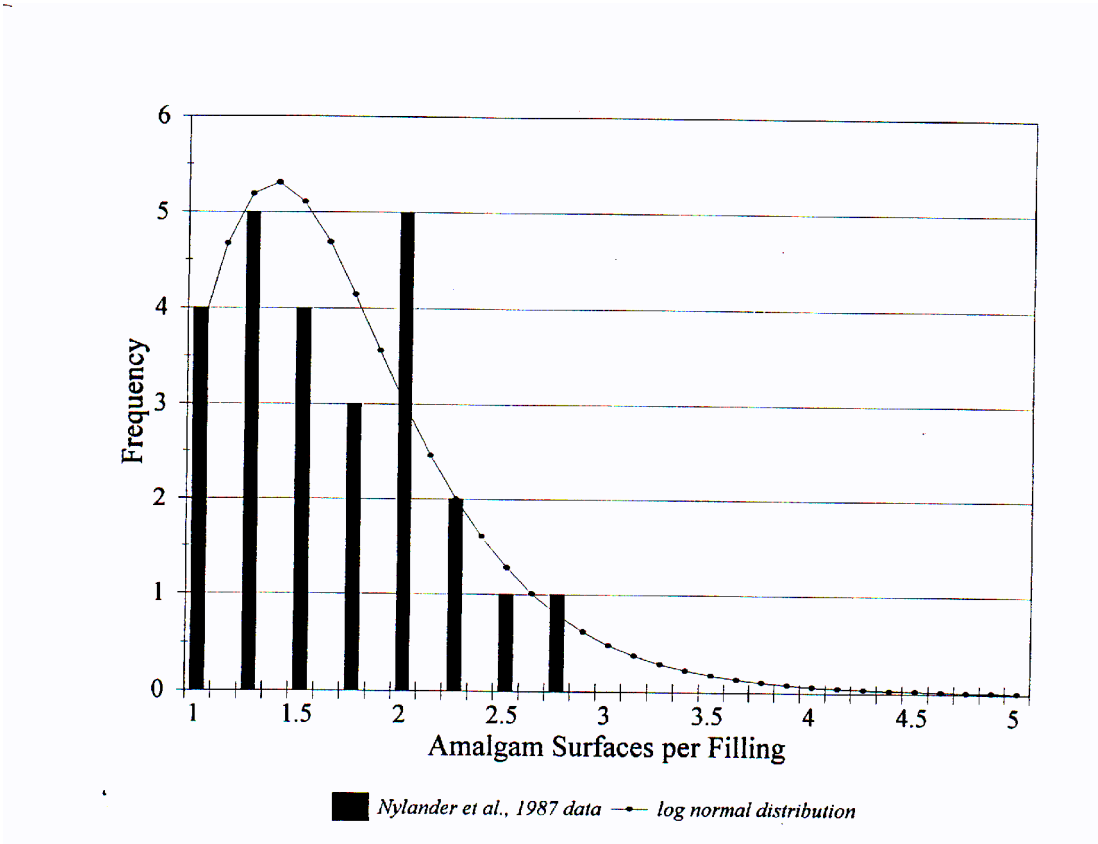


Figure 5.9. Estimated probability density function of the number of amalgam surfaces per filled tooth (after Nylander et al. (1987).



defining log-normal probability density distributions for each age group are summarized in Table 5.1. For each distribution, a limit of 1440 minutes per day was established as the maximum.

Table 5.1 Assumptions for time spent eating.

Age group	Mean time spent eating ± s.d. (min/day)
Toddlers (3 to 4 yrs)	88.3 ± 68.9
Children (5 to 11 yrs)	72.4 ± 56.5
Teens (12 to 19 yrs)	69.5 ± 54.2
Adults (20 to 59 yrs)	90.7 ± 70.7
Seniors (60+yrs)	116 ± 90.5

In addition to the actual amount of time spent eating, it is necessary to define how many times per day food is eaten, since each eating episode is followed by a passivation period, during which the Hg release rate declines from the stimulated value to the baseline value. There do not appear to be any reliable data pertaining to the number of meals and snacks eaten by Canadians of various ages, so probability density functions were chosen arbitrarily. Triangular probability distributions with a minimum of zero meals and/or snacks per day and a maximum of 10 meals and/or snacks per day were assigned for each age group. For toddlers the most likely value was assumed to be five meals and/or snacks per day; for all other age groups the most likely value was assumed to be three meals and/or snacks per day.

5.2.10 Tooth brushing habits

Patterson et al. (1985) demonstrated that normal tooth brushing causes temporary increases in the emission of Hg vapour from dental amalgam. Although Patterson et al. (1985) did not report how long such increases persist, it is not unreasonable to assume that the effect lasts about as long as the increase brought about by eating, since both tooth brushing and eating are forms of mechanical abrasion of tooth surfaces.

There do not appear to be any reliable data pertaining to the frequency with which Canadians brush their teeth, so probability density functions were chosen arbitrarily. Triangular probability distributions with a minimum of zero times per day and a maximum of three times per day were assigned for each age group. For toddlers (aged 3 and 4) the most likely value was assumed to be once per day; for all other age groups the most likely value

was assumed to be twice per day. Because the triangular probability distributions are continuous rather than discrete, each generated number of tooth brushings was rounded to the nearest whole number.

In the absence of any reliable data pertaining to the duration of tooth brushing, it was assumed that each episode of tooth brushing lasts between 1 and 3 minutes, with any value in this range considered equally likely.

5.2.11 Sleeping habits

The number of hours per day spent sleeping was modelled with normal distributions. Weighted averages were calculated for each age group from data presented by Wiley et al. (1991a,b) and were used as the mean values. The ratio of standard deviation to mean (i.e., the coefficient of variability) for adults was reported to be 26% (Wiley et al. 1991b). In the absence of data concerning standard deviations for other age groups, the same coefficient of variability was assumed for all age groups. The input variables for each age group are summarized in Table 5.2.

Table 5.2. Assumptions for time spent sleeping.

Age group	Mean time spent sleeping (hours/day)	Standard deviation (hours/day)
Toddlers (3 to 4 yr.)	10.51	2.78
Children (5 to 11 yr.)	9.86	2.60
Teenagers (12 to 19 yr.)	9.14	2.41
Adults (20 to 59 yr.)	8.40	2.22
Seniors (60 yr. and up)	8.52	2.25

5.2.12 Oral breathing habits

For the purposes of this study, separate probability density functions were assigned to define oral breathing habits while awake versus oral breathing habits while asleep. The same set of probability density functions was used for all age groups.

Gleeson et al. (1986) studied the oral breathing habits of sleeping subjects. During Rapid Eye Movement (REM) sleep, the amount of oral breathing among the subjects ranged from 0% to 56%. During non-REM sleep, the amount of oral breathing ranged from 0% to 53%. Data for REM and non-REM sleep from the Gleeson et al. (1986) study were combined into a frequency distribution (Figure 5.10). In this assessment an exponential probability density function with a maximum of 1, minimum value of 0 and a rate parameter of 7 was used to represent the amount of oral breathing by normal subjects during sleep. The shape of this function is superimposed on Figure 5.10 for comparison. Both the Gleeson et al. (1986) data and the exponential distribution yield mean values of approximately 15%.

The oral breathing habits of non-sleeping subjects appear more variable than those of sleeping subjects. Quiet activity is dominated by nasal rather than oral breathing, as shown by Uddstromer (1940), Camner and Bakke (1980), and Gleeson et al. (1986). Oral breathing ratios for subjects engaged in silent reading (Camner and Bakke, 1980), watching television (Gleeson et al., 1986) and resting silently before and after bouts of vigorous activity (Group II subjects from Uddstromer, 1940) are presented on Figure 5.11. The average oral breathing ratio for the data shown on Figure 5.11 is approximately 5.1%. For the purposes of this assessment, oral breathing during quiet activity was represented with a two-stepped custom probability density distribution, with ranges 0% to 5.1% and 5.1% to 100%. The probabilities assigned to the lower and upper ranges were 0.949 and 0.051, respectively. These probabilities were determined by keeping the probabilities within each range constant and defining the overall mean of the custom distribution to be 5.1%.

More oral breathing is associated with talking than with quiet activity (Camner and Bakke, 1980). A frequency distribution for subjects engaged in conversation and counting aloud from the Camner and Bakke (1980) study is presented on Figure 5.12. The average oral breathing ratio for these subjects was approximately 70%. For this assessment, the data were approximated with a normal distribution with a minimum of 0%, a maximum of 100%, a mean of 72% and a standard deviation of 18%. The shape of this distribution, which has an overall mean of approximately 70%, is shown on Figure 5.12 for comparison.

There do not appear to be any reliable data of the amount of time people spend talking or otherwise actively engaged in conversation. In the absence of such information, it was arbitrarily assumed for the purposes of this assessment that people spend between 10% and 80% of their awake time engaged in conversation, with any value in between considered equally likely.

The overall time-weighted average of oral breathing while awake was calculated in the assessment as:

$$F_a = f_c \bullet F_c + (1-f_c) \bullet F_q$$

where

F_a = the time-weighted average oral breathing ratio while awake;
f_c = the fraction of awake time spent in conversation;
F_c = the oral breathing ratio while engaged in conversation;
F_q = the oral breathing ratio during quiet activity.

Figure 5.10 Percent breathing done orally while asleep (from Gleeson et al. 1986).

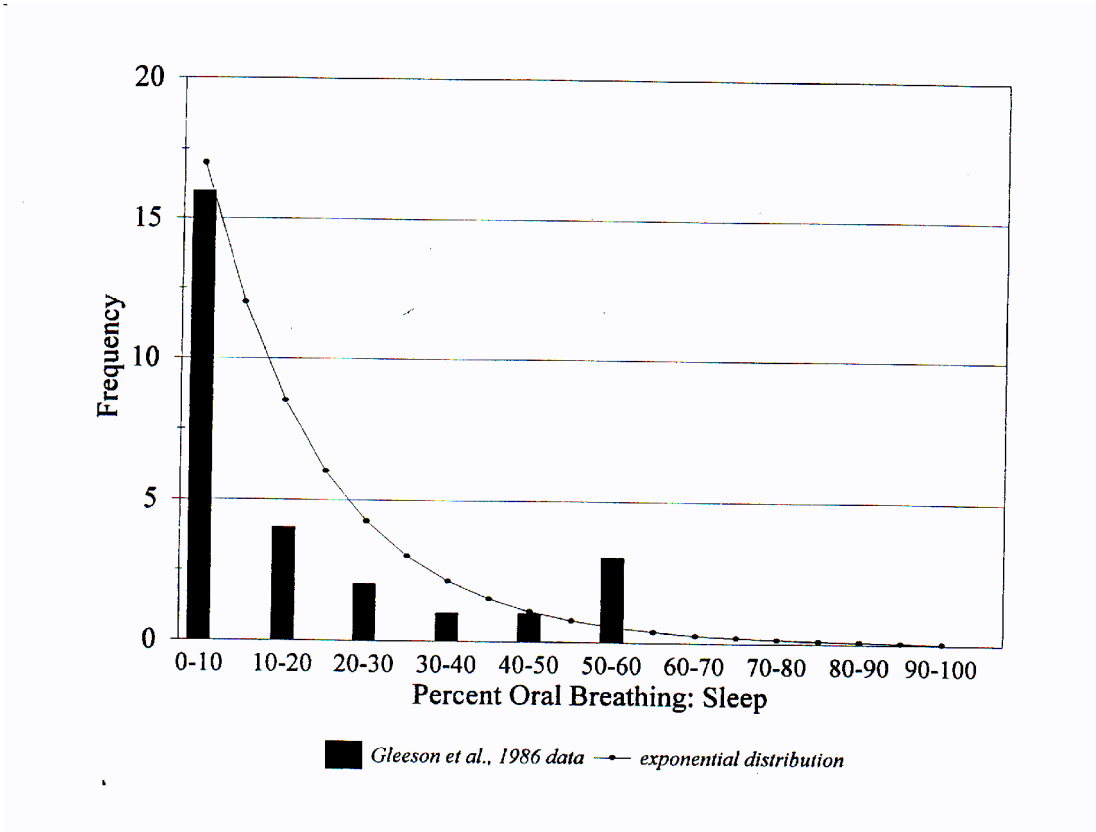


Figure 5.11 Percent breathing done orally during quiet activity (from Uddstromer, 1940; Camner and Bakke, 1980; and Gleeson et al. 1986).

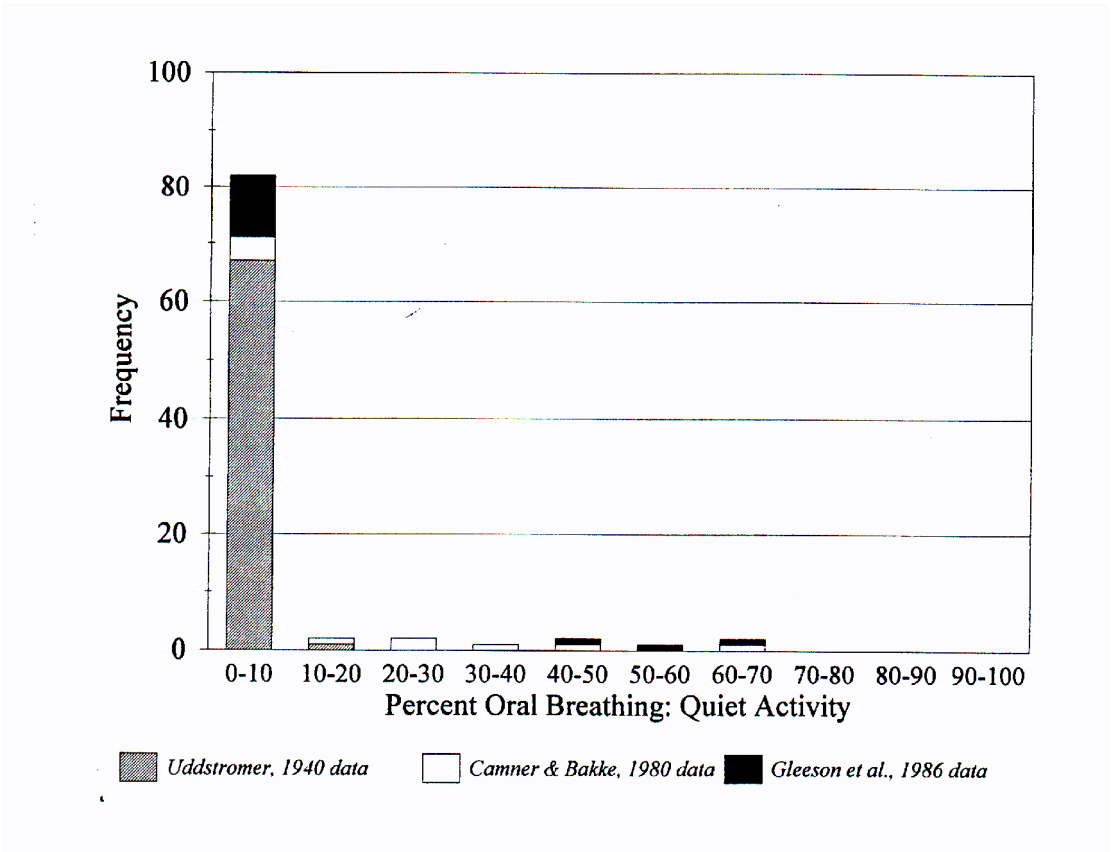
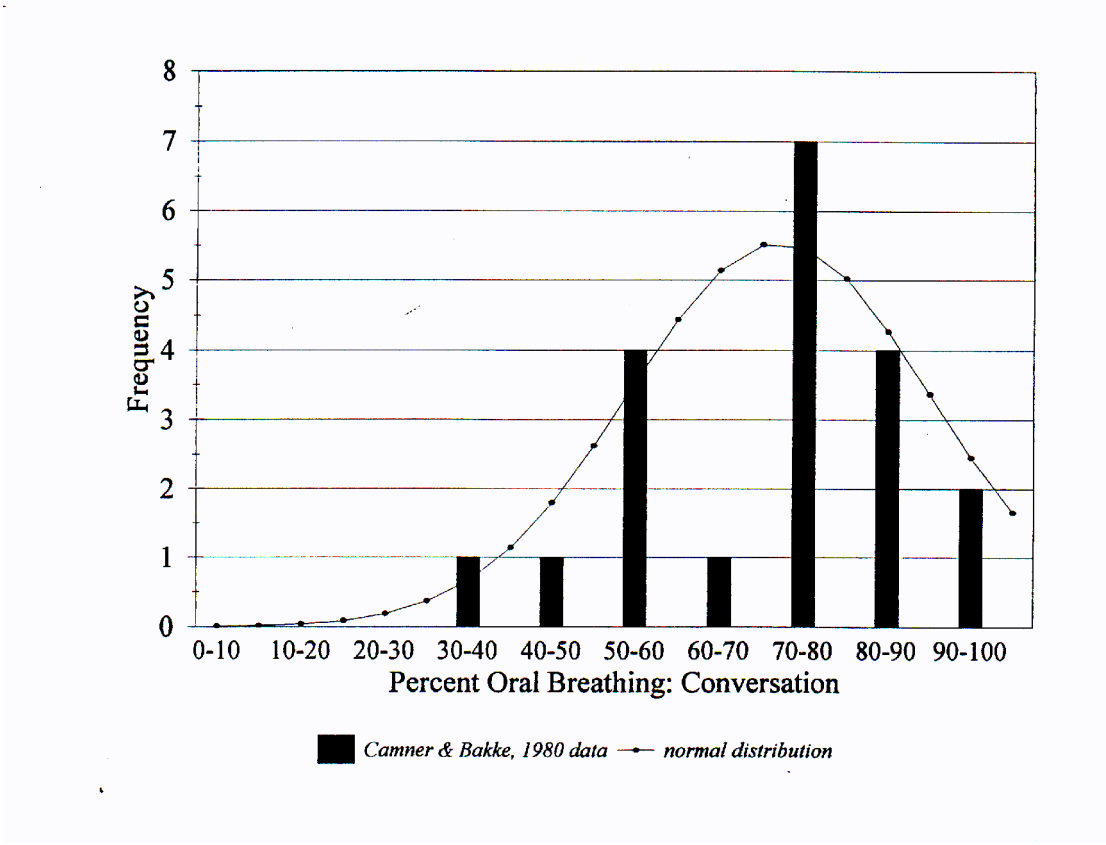


Figure 5.12 Percent of breathing done orally during conversation (from Camner and Bakke, 1980).



5.2.13 Body weight

In this assessment, body weights for the five age groups were described by log-normal probability distributions. Assumptions concerning these distributions are presented in Table 5.3.

Table 5.3. Assumptions for body weight.

Age Group	Mean body weight ± s.d. (kg)	mean(ln body weight) ± s.d. ln(kg)
Toddlers (3 to 4 yr.)	18 ± 1.2	2.88 ± 0.15
Children (5 to 11 yr.)	27 ± 1.3	3.29 ± 0.26
Teenagers (12 to 19 yr.)	60 ± 13.5	4.07 ± 0.22
Adults (20 to 59 yr.)	71± 14.4	4.24 ± 0.20
Seniors (60 yr. and up)	71± 15.0	4.23 ± 0.22

Body weight data for children, teens, adults and seniors were derived from Stephens and Craig (1990). Stephens and Craig (1990) did not report data for toddlers. For this latter age group, mean body weight was modified from 1970 NCS data (HC unpublished), adjusting for a 2.9% increase in mean ln-transformed body weight in children (5 to 11 yrs) between 1970 (HC unpublished) and 1988 Stephens and Craig (1990). Standard deviation of mean ln(body weight) was assumed to be equivalent to that measured in 1970.

5.2.14 Factors not considered

Although a variety of factors have been incorporated into this assessment which will influence the rate of Hg release from amalgam fillings and subsequent exposure, a number of other factors have not been incorporated, due primarily to a lack of adequate quantitative data. These factors include: 1) consumption of hot beverages (such as coffee, tea, etc.) which may increase the rate of Hg emission from amalgam due to the effect of temperature (Fredin 1994); 2) habitual gum chewing, which has been shown to enhance Hg emission from amalgam like other forms of stimulation; 3) bruxism; 4) conditions which result in unusually high rates of oral breathing, such as chronic sinus congestion, regular aerobic physical exercise and/or exertion, etc.

5.2.15 Sensitivity analysis

A sensitivity analysis was conducted using methods described by Decissioneering (1993) in order to evaluate the relative influence of the different model variables to overall variance is estimates of exposure.

5.2.16 Results

Ranges of estimated total exposure from both inhalation and ingestion of Hg from amalgam, and corresponding probabilities for toddlers, children, teens, adults and seniors, are illustrated in Figures 5.13 through 5.17. The distributions are positively skewed indicating

that most people will experience exposure toward the lower end of the indicated ranges. For each age group, about 60% of the Hg exposure was attributed to inhalation of Hg vapour, and 40% attributed to the ingestion of Hg^{2+} in saliva (see Table 5.4).

Table 5.5 summarizes the results of the exposure assessment for each age group. For adults (aged 20 to 59 years) with amalgam fillings, a mean exposure of 3.74 µg/day was estimated; this is higher than the estimates for any of the other age groups. On a per kg body weight (bw) basis, estimates of total Hg exposure were: toddler 0.08 µg/kg bw/day; child 0.07 µg/kg bw/day; teen 0.04 µg/kg bw/day; adult 0.05 µg/kg bw/day; senior 0.04 µg/kg bw/day.

Because the number of amalgam fillings in one's mouth has such a dramatic effect on the amount of exposure, and hence, risk, the Monte Carlo simulation was re-run for discrete numbers of fillings. The results, on a per kg body weight basis, are summarized in Table 5.6.

The ten most significant variables for adult exposure, i.e., the ten parameters that have the greatest effect on the variability of the results, are presented in Figure 5.18 (results were similar for other age groups). For all age groups, the most sensitive variables in determining the amount of exposure were the number of fillings, followed by the value of the Hg release rate per filling surface, and the stimulation magnification factor.

Table 5.4. Percent of daily total exposure from ingestion of Hg^{2+} from amalgam - Assessment I (after Olsson and Bergman, 1992)

Statistic		Toddler (%)	Child (%)	Teen (%)	Adult (%)	Senior (%)
Mean		42	42	42	41	41
Median (approx.)		41	41	41	40	40
Mode (approx.)		41	38	38	37	43
Standard Deviation		17	17	17	17	17
Percentiles:	5%	17	16	16	16	16
	10%	21	21	20	20	20
	20%	27	26	26	25	25
	30%	32	32	31	30	30
	40%	36	36	36	35	35
	50%	41	41	41	40	40
	60%	46	46	46	45	45
	70%	52	51	51	50	51
	80%	58	58	57	57	57
	90%	66	66	65	65	65
	95%	72	71	71	71	71

Table 5.5. Results of total exposure - Assessment I (after Olsson and Bergman, 1992)

Statistic		Toddler (µg/day)	Child (µg/day)	Teen (µg/day)	Adult (µg/day)	Senior (µg/day)
Mean		1.43	1.72	2.49	3.74	2.78
Median (approx.)		0.99	1.10	1.58	2.43	1.51
Mode (approx.)		0.62	0.70	0.73	0.42	0.26
Standard Deviation		1.54	2.05	2.92	4.41	3.73
Percentiles:	5%	0.18	0.17	0.20	0.24	0.18
	10%	0.28	0.26	0.33	0.42	0.28
	20%	0.45	0.43	0.58	0.82	0.49
	30%	0.61	0.62	0.87	1.28	0.75
	40%	0.78	0.83	1.19	1.81	1.08
	50%	0.99	1.10	1.58	2.43	1.51
	60%	1.22	1.42	2.08	3.21	2.10
	70%	1.53	1.87	2.74	4.16	2.91
	80%	2.06	2.55	3.71	5.67	4.18
	90%	3.05	3.82	5.58	8.44	6.68
	95%	4.19	5.26	7.82	11.51	9.30

Table 5.6 Average exposure (µg/kg bw/day) estimates for fixed numbers of fillings.

Age group	Number of fillings					
	1	2	4	8	12	20
Toddler	0.025	0.049	0.098	0.197	--[a]	--[a]
Child	0.017	0.033	0.066	0.132	0.199	--[a]
Teen	0.007	0.015	0.029	0.058	0.087	0.146
Adult	0.006	0.013	0.025	0.051	0.076	0.127
Senior	0.007	0.013	0.027	0.054	0.081	0.135

Figure 5.13. Distribution of estimated Hg exposure (µg Hg/day) for toddlers with amalgam fillings.

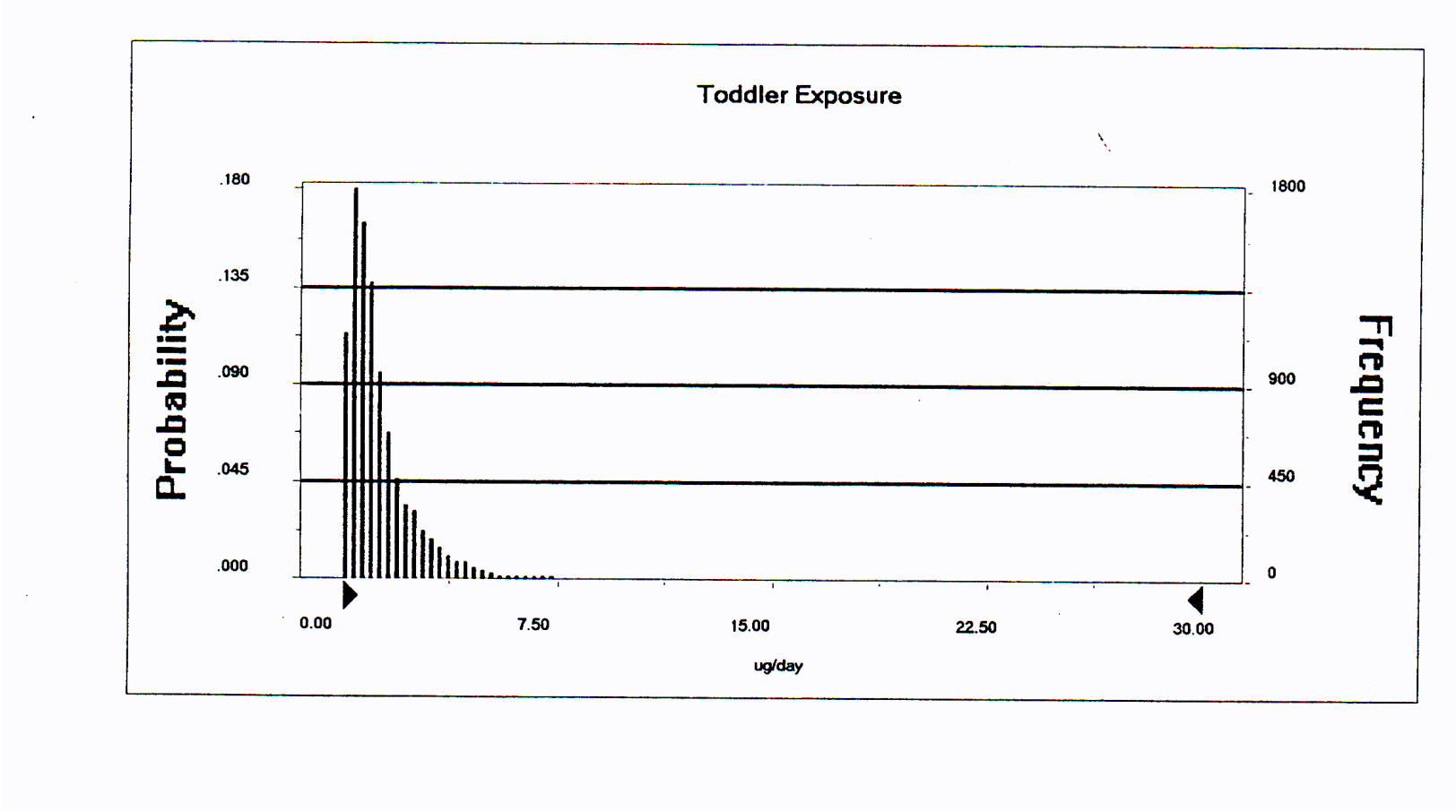


Figure 5.14. Distribution of estimated Hg exposure (µg Hg/day) for children with amalgam fillings.

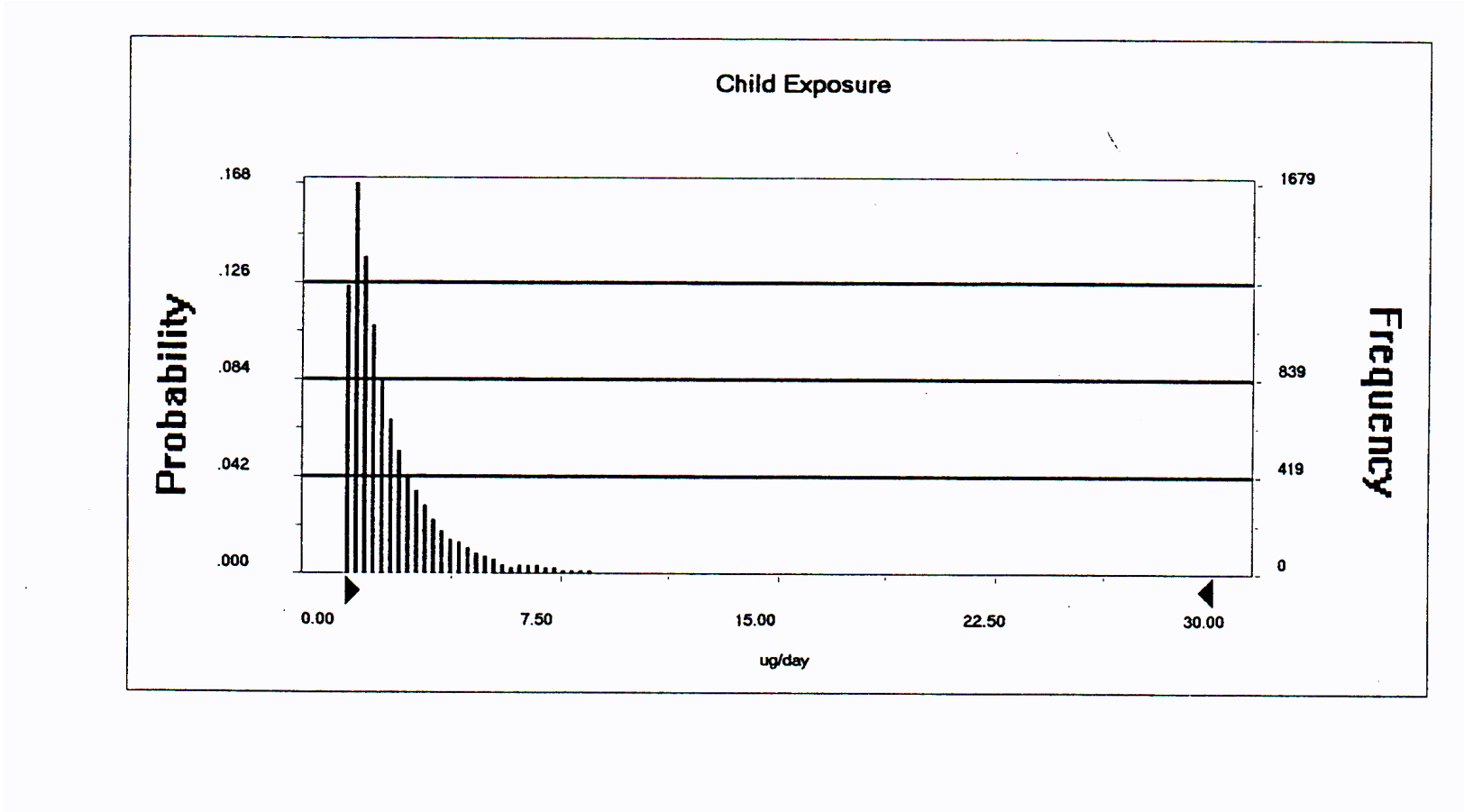


Figure 5.15. Distribution of estimated Hg exposure (µg Hg/day) for teens with amalgam fillings.

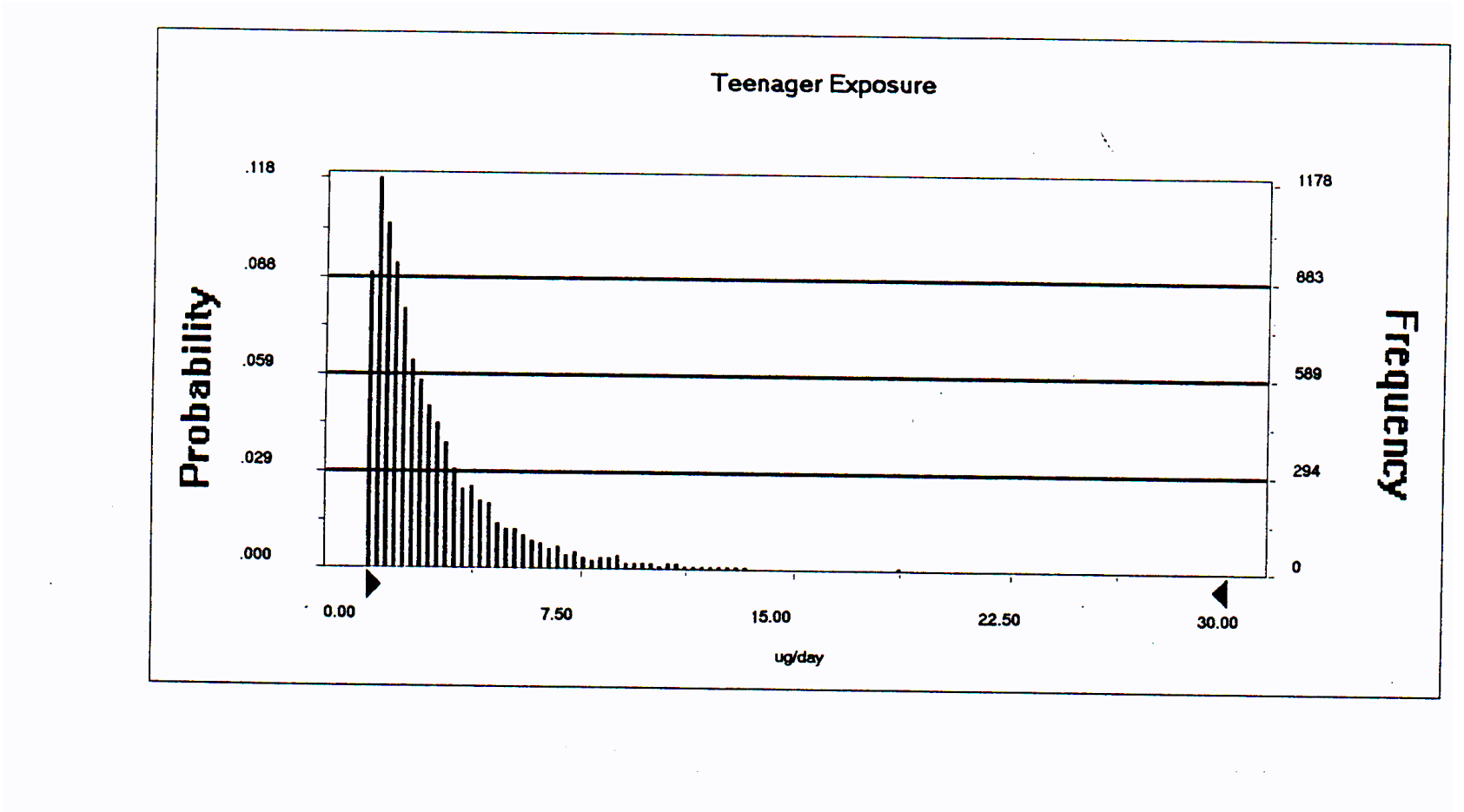


Figure 5.16. Distribution of estimated Hg exposure (µg Hg/day) for adults with amalgam fillings.

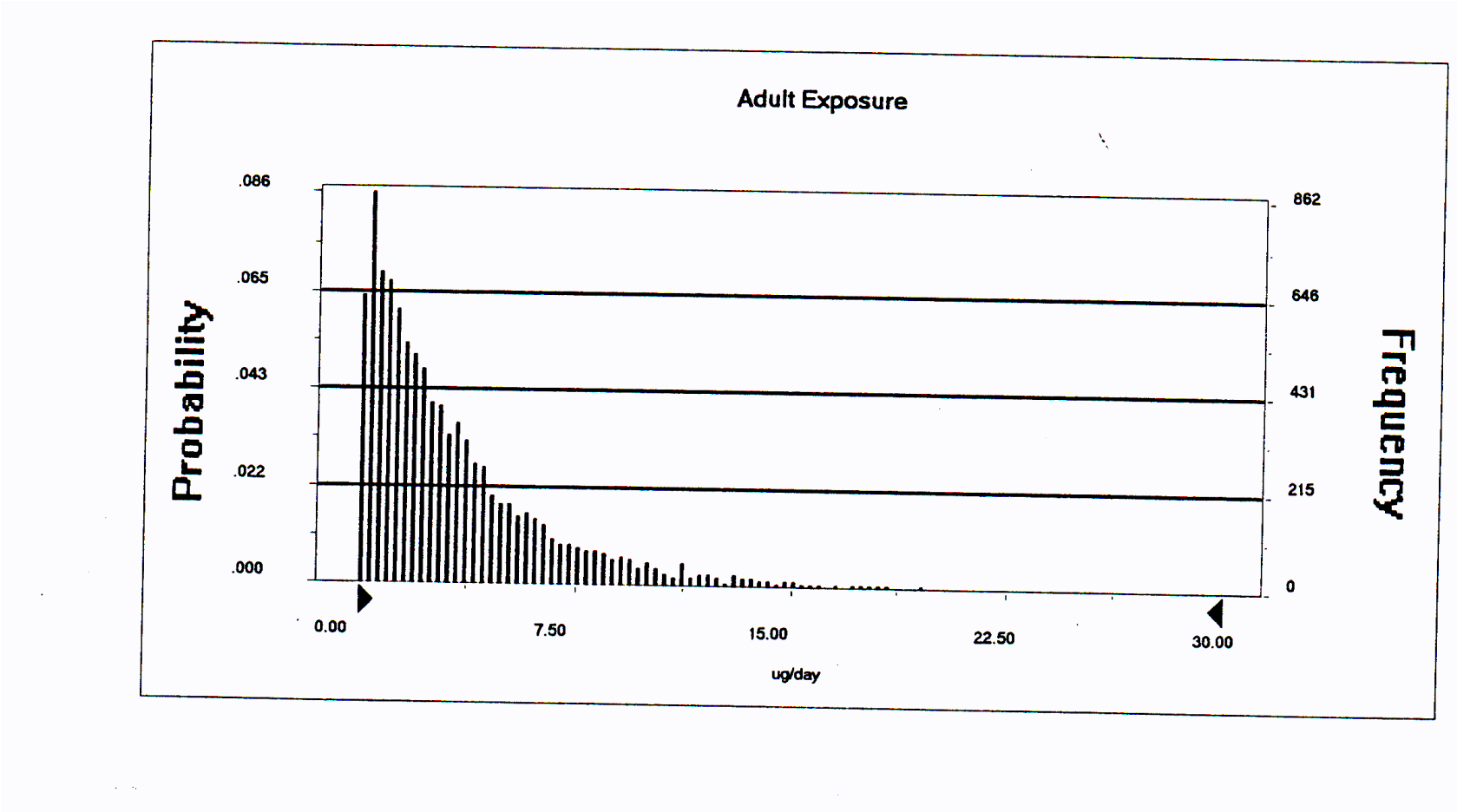


Figure 5.17. Distribution of estimated Hg exposure (µg Hg/day) for seniors with amalgam fillings.

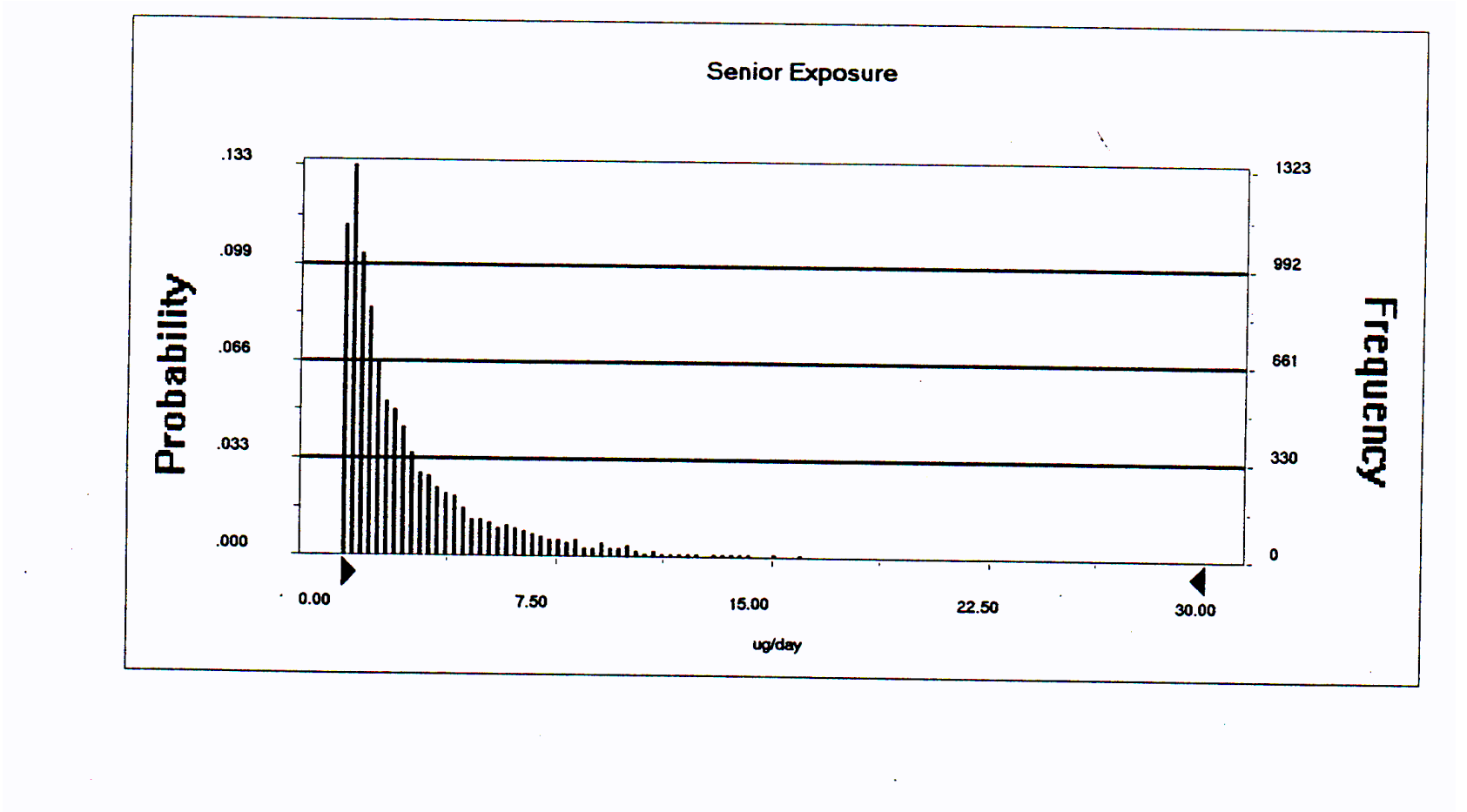
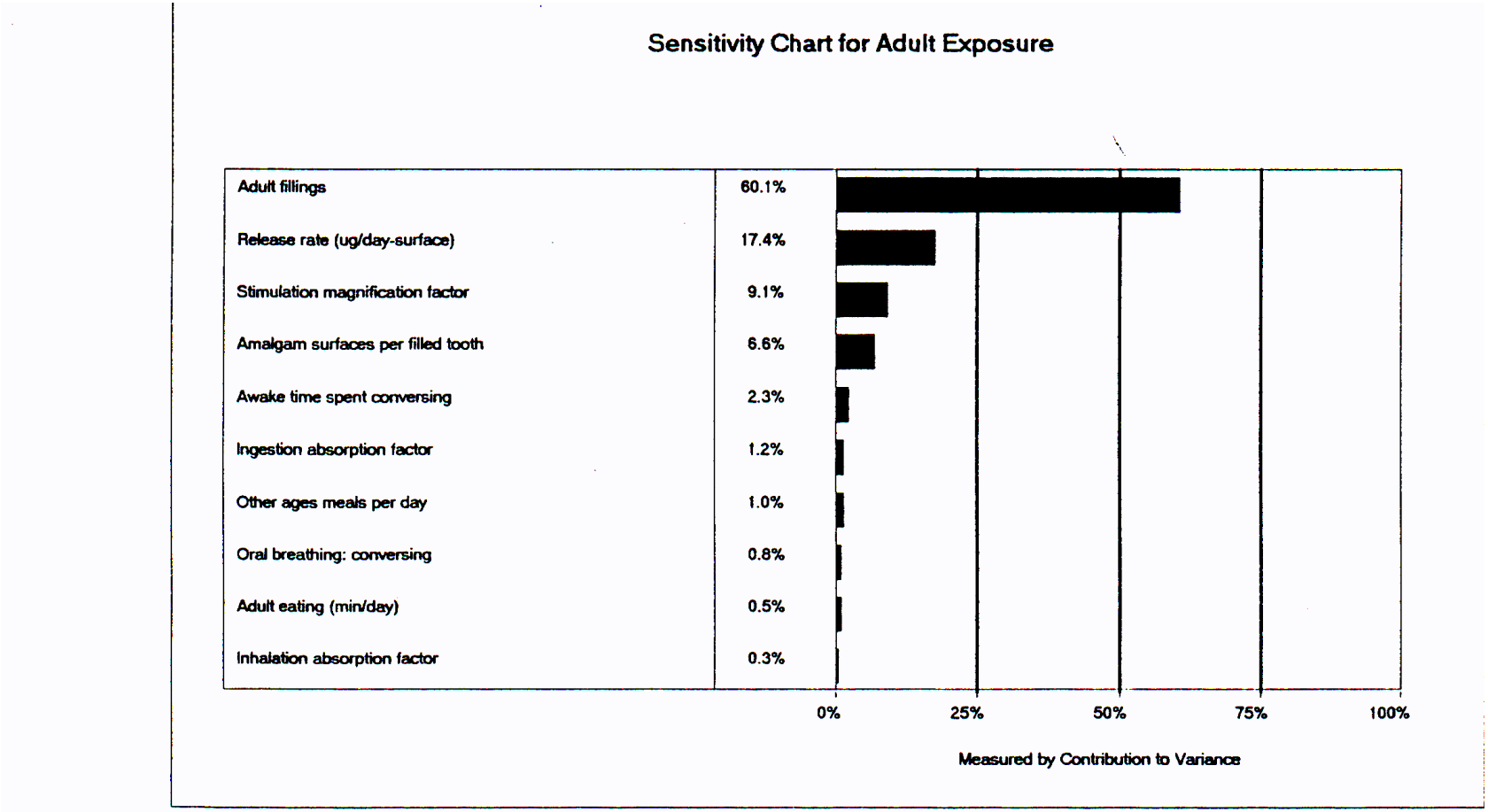


Figure 5.18. Sensitivity analysis for adult exposure. Parameters listed are the 10 most significant factors influencing estimated exposure.



5.3 Exposure Assessment II - after Richardson et al. (1995)

Richardson et al. (1995) employed a deterministic (i.e. point estimate), multimedia approach to estimate Hg exposure for members of the general population in Canada. Total exposure to Hg was estimated as the sum of exposures to Hg^0, Hg^{2+} and methylHg from inhalation of air, ingestion of soil, water and foods, and intake from dental amalgam (inhalation only). Exposure was calculated for both delivered dose and absorbed dose, adjusted for differential absorption for each Hg species via each route of exposure. Richardson et al. (1995) estimated that adult Canadians with 7 amalgam-filled teeth had a total intake of 7.7 µg Hg/day (0.11 µg Hg/kg body weight/day), of Hg^0, Hg^{2+} and methylHg, from air, water, soil, food, and dental amalgam, via inhalation and ingestion. This equated to an absorbed dose of 5.3 µg Hg/day (0.076 µg Hg/kg bw/day). Fish consumption accounted for much of this exposure (27% of intake, 40% of absorbed dose), in the form of methylHg. However, dental amalgam appeared to account for a greater proportion of total Hg exposure than fish consumption. Exposure from amalgam was estimated for delivered and absorbed doses (of Hg^0) at 2.81 and 2.25 µg Hg^0/day, respectively, for 7 filled teeth. This represented 36% of total Hg intake and 42% of absorbed dose. Exposures for four other age groups of the population were also evaluated.

The estimates of exposure by Richardson et al. (1995), although the most recent assessment of Canadian exposure to Hg, represented only an estimate for a hypothetical 'average' Canadian. Exposure will vary from individual to individual, given differences in individual characteristics such as number of filled teeth, eating and breathing rates, spatial variation in Hg levels in the various media, etc. That assessment did not provide any information on the population distribution of exposure. In order to provide such a distribution, a stochastic exposure assessment approach (Burmaster and von Stackelberg, 1991; Thompson et al. 1992) has been applied to the general methods of Richardson et al. (1995). Probability density functions were used to represent input variables for which more than one value was possible. The characterization of each variable's probability density function, and the rationale for selecting each, is discussed below.

5.3.1 Exposure from dental amalgam

The distribution of numbers of filled teeth per age group are presented and discussed in Section 5.2.7. Assuming one filling per filled tooth, the regression presented by Skerfving (1991) (Figure 5.19) was used to determine the urine concentration corresponding to each number of fillings. It was assumed that the relationship between number of fillings and urine Hg concentration was independent of age, as no data were available to suggest otherwise. Variability about the regression line in Skerfving (1991), represents individual variability in the uptake, absorption and excretion of Hg from amalgam. These data were transcribed and then re-transformed to natural logarithms for easier data manipulation. The slope of this relationship was entered as a variable with a normal distribution with a mean of 0.096 ln(µg Hg/g creatinine)/filling and a standard error of 0.01. The intercept of that relationship was also entered as a normally-distributed variable with mean of -0.8 ln(µg Hg/g creatinine) and standard error of 0.23, as defined by the data (see Figure 5.19)

To estimate the dose absorbed to give rise to the urine Hg contamination described by Skerfving (1991), it was necessary to employ a relationship between urine Hg levels and inhalation exposure. Roels et al. (1987) reported a strong linear association between workroom air and urine Hg in workers. That regression model was redefined, specifying a Y-intercept equal to 0.45 μg Hg/g creatinine in urine, on the assumption that non-occupationally exposed individuals (not included in the regression analysis reported by Roels et al. 1987) would have a background urine Hg concentration the same as that reported by Skerfving (1991). This slope was assumed to be normally-distributed with a mean of 1.21 ± 0.12 (defined by the data; see Figure 5.20). It was necessary to convert the workroom air measurements reported by Roels et al. (1987) to an equivalent absorbed dose of Hg. To do this, an occupational inhalation rate was assumed with a triangular distribution with a most likely value of 6.6 m^3 per 8 hour work shift, a minimum value of 1.1 and a maximum of 13.2 m^3 per 8 hour work shift (U.S. EPA, 1989). Parameters used to describe absorption of Hg^0 by the lung were identical to that described in Section 5.2.5. Combining these with the relationship of Skerfving (1991) provided a distribution of estimated Hg exposure as a function of the number of amalgam fillings.

Figure 5.19. Association between number of amalgam-filled teeth and urine Hg concentration (after Skerfving 1991). Curved lines represent the 99% confidence limits on the regression line.

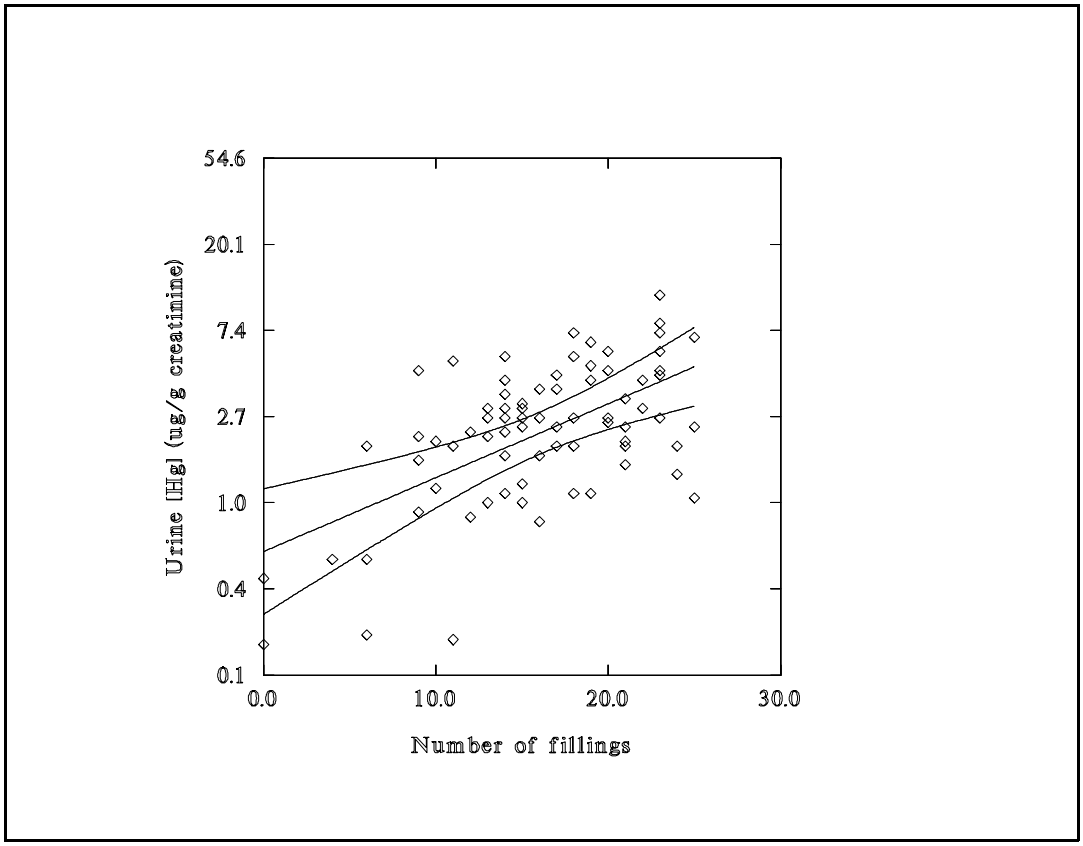
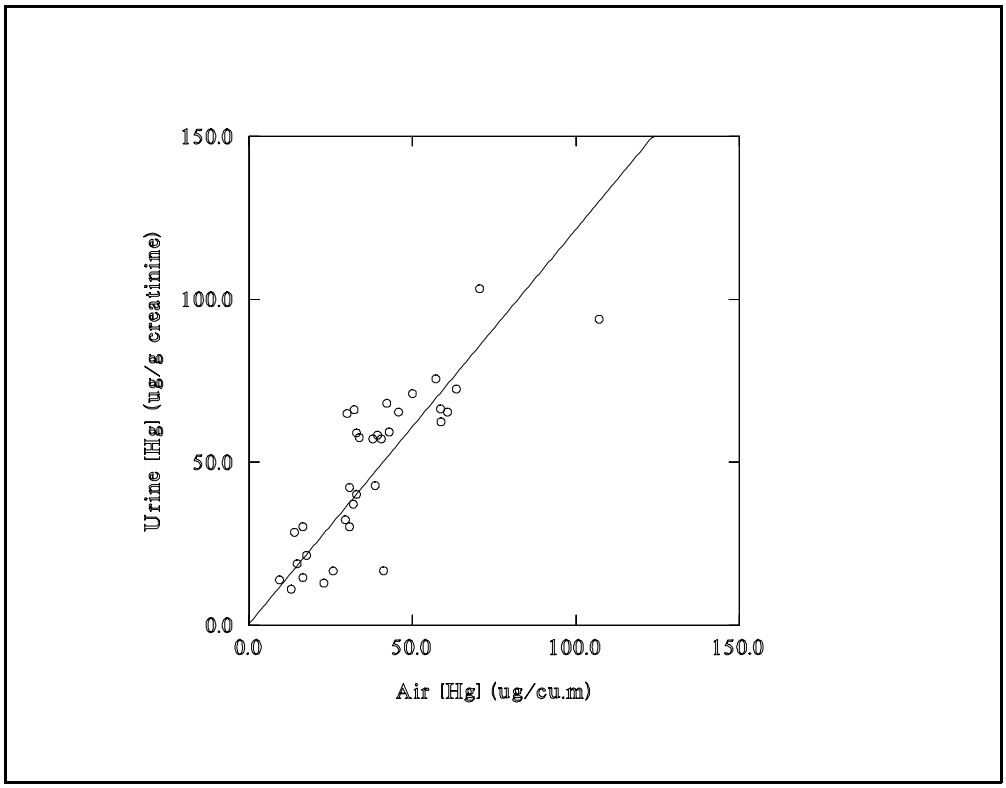


Figure 5.20. Modified association between inhalation exposure and urine Hg concentration (after Roels et al. 1987), forcing a Y intercept of 0.45 µg Hg/g creatinine. The equation for this modified regression is: urine[Hg] (µg Hg/g creatinine) = 0.45 + 1.21*Air[Hg] (µg Hg/m^3). The standard error of the slope is 0.12.



5.3.2 Body weight

Distributions of body weight employed for the five age groups are described in Section 5.2.13.

5.3.3 Inhalation rate

Empirically-derived probability density functions for 24 hour inhalation rate do not exist. These distributions can be generated, however, based on measured minute volumes for various activity levels (resting, light, moderate, heavy activity, etc.) combined with data on time spent at each of these activity levels. The resulting distributions from combining time activity and minute volume data were normal and had the following characteristics (from Allan 1995):

Table 5.7. Assumptions for 24 hour inhalation rate (after Allan, 1995).

Age group	Mean 24 hour inhalation rate ± s.d (m^3)
Toddlers (3 to 4 yr.)	8.8 ± 2.0
Children (5 to 11 yr.)	14.4 ± 3.2
Teenagers (12 to 19 yr.)	15.5 ± 3.9
Adults (20 to 59 yr.)	16.7 ± 4.3
Seniors (60 yr. and up)	13.9 ± 2.6

5.3.4 Water ingestion rates

Water ingestion rates for each age group were derived from EHD (1981), based on a survey of drinking water consumption conducted in Canada in 1977 and 1978. This was the only national drinking water consumption survey conducted in North America. These data included the consumption of tap water-based beverages such as coffee and tea. The distributions were log-normal and had the following characteristics:

Table 5.8. Assumptions for daily tap water ingestion (from EHD 1981).

Age group	mean water consumption ± s.d. (L/day)
Toddlers (3 to 4 yr.)	0.90 ± 0.4
Children (5 to 11 yr.)	1.00 ± 0.4
Teenagers (12 to 19 yr.)	1.30 ± 0.5
Adults (20 to 59 yr.)	1.47 ± 0.6
Seniors (60 yr. and up)	1.57 ± 0.6

5.3.5 Consumption of various foods

The Nutrition Canada Survey (HWC 1977) collected data on the consumption of 180 different foods or food groups from nearly 13,000 Canadians. Based on the availability of Hg contamination data for commercial foods other than fish (see Section 5.3.10), 140 of these foods or food groups were employed in this analysis. Of these, 8 foods (liver, rice, canned mushrooms, pork composite dishes (pork chow mein), other nuts (pecans), spinach, prunes, and raisins) had consistently detectable levels of Hg and, therefore, were treated individually. The others were grouped into 11 general categories (see Table 5.10). The distributions for consumption of each of these 19 foods, for all five age groups, were based entirely on the empirical data (HC, unpublished) collected as part of the Nutrition Canada Survey. The data were too voluminous to present or append here, but are available from the Environmental Health Directorate, Health Canada.

Data on consumption of saltwater fish, freshwater fish and shellfish were also collected as part of the Nutrition Canada Survey and these data were also employed to define distributions of consumption patterns for these foods.

5.3.6 Ingestion of soil

Data pertaining to intentional or unintentional soil ingestion are limited. Therefore, distributions for soil ingestion rate were established arbitrarily. Based on available data, Health Canada (HC 1994) has proposed average intake rates for each age group. These values were employed as mean values for log-normal distributions with the following characteristics:

Table 5.9. Assumptions for soil ingestion rate.

Age group	ln(mean soil ingestion rate (mg/day)) ± s.d.
Toddlers (3 to 4 yr.)	4.07 ± 0.59
Children (5 to 11 yr.)	3.38 ± 0.59
Teenagers (12 to 19 yr.)	2.98 ± 0.20
Adults (20 to 59 yr.)	2.98 ± 0.20
Seniors (60 yr. and up)	2.98 ± 0.20

5.3.7 Ambient and indoor air

Distribution parameters for Hg concentration in ambient air were based on the results of Schroeder and Jackson (1987) and OMEE (1994). Schroeder and Jackson (1987) reported concentrations of several Hg species in the air in and around Toronto, Ontario during the fall of 1981. The limited data (total n=25) indicated a minimum of 3 ng Hg/m^3, a maximum of 27 ng Hg/m^3 and a mean of 10 ng Hg/m^3. OMEE (1994) reported 11 to 18 serial half hour measurements of total Hg in the air of Windsor, Ontario on six consecutive days from July 25 to August 2, 1990. Individual half hour air concentrations ranged from below detection (n=1; detection limit = 10 ng Hg/m^3) to 160 ng Hg/m^3. Daily arithmetic averages ranged from 19.3 to 45.6 ng Hg/m^3, with a grand arithmetic mean of 28.8 ± 19.9 ng Hg/m^3.

Given the limited available data, a uniform distribution for Hg air concentration was assumed, from a minimum of 3 to a maximum of 46 ng Hg/m^3. It was also assumed that Hg in ambient air was 75% Hg^0, 20% methyl Hg and 5% Hg^{2+} (Schroeder and Jackson 1987).

No published or unpublished data could be located on Hg levels in indoor air of Canadian homes. Foote (1972) reported very limited U.S. data on the levels of Hg in the indoor air of homes and office buildings, ranging from 5.0 to 3,070 ng/m^3 (n=19). However, many of the rooms monitored had been recently painted with latex-based paints containing Hg as a preservative. As the use of Hg as a preservative in interior paint was voluntarily discontinued in Canada as of January 1991 (B. Tom, Health Canada, pers. com.), these data were not considered relevant to current Hg exposure via indoor air.

Agocs et al. (1990) and Beusterien et al. (1991) reported indoor air Hg data for 10 homes in Michigan (1989) and 16 homes in Ohio (1990), respectively, where no Hg-containing paint had been applied within the preceding 18 months. In both studies, the median Hg levels were non-detected when measured by atomic absorption spectro-photometry (reported detection limit (DL)=0.5 $nmol/m^3$). Analysis of 4 homes by cryogenic gas chromatography with atomic fluorescence detection (reported DL = 3 ng/m^3) measured Hg at a median level of 52 ng Hg/m^3 (range: 36-107 ng Hg/m^3) (Beusterien et al., 1991). Due to the small number of measurements reported, the Hg concentration in indoor air was assumed to have a uniform distribution with a minimum value of 30 ng Hg/m^3 and a maximum value of 110 ng Hg/m^3. It was assumed that Hg in indoor air is 100% Hg^0 (Beusterien et al. 1991).

5.3.8 Drinking water

82% of urban dwelling Canadians (63% of total population) receive treated drinking water (Tate and Lacelle, 1992). Therefore, data on Hg levels in treated drinking water supplies were considered the most representative source of data for this assessment. The Ontario Ministry of Environment and Energy (OMEE) analyzed 1,355 samples of treated drinking water from 134 sites in 1991/92 (OMEE, 1993) and all but 8 had total Hg levels below the limit of detection (0.02 µg Hg/L). Other provinces have routinely reported non-detected Hg levels in drinking water but used methods with a higher detection limit than that employed by OMEE. For this assessment a uniform distribution ranging from a minimum of 0 to a maximum of 0.02 µg Hg/L was assumed. Hg in drinking water was assumed to be 25% methyl Hg and 75% Hg^{2+} (Schintu et al., 1989).

5.3.9 Soil and dust

Data were collected between 1980 and 1990 by the Geological Survey of Canada (total n= 1,684 soil samples; range: 0.002-1.53 µg Hg/g soil), from Ontario and western Quebec (Kettles and Shilts, 1983; Kettles 1988a,b, 1990). These data were used to characterize soil concentration, which was log-normally distributed with a mean of -2.73 ± 0.90 ln(µg Hg/g soil).

No reliable published data on Hg levels in the dust of Canadian or American homes were located. Therefore, it was assumed that indoor dust was identical to soil in chemical composition.

5.3.10 Commercial foods other than fish

No systematic or routine Hg monitoring has been conducted on the Canadian food supply since 1970/71 except for fish and fish products destined for commercial sale (B. Huston, Foods Directorate, Health Canada, pers. com.). Therefore, data from 37 recent (1982 to 1991) U.S. total diet surveys of Hg levels in 231 food stuffs (E.L. Gunderson, USFDA, unpublished) were used, for all foods other than fish and shellfish. All foods were analyzed for Hg with a detection limit of 0.001 μg Hg/g.

Hg contamination data employed in this assessment are summarized in Table 5.10. Levels were low in all cases. These foods fell into two general categories: 1) Hg detected in less than half of the samples analyzed (i.e. median value below detection); 2) Hg detected in most or all of samples analyzed (i.e. median value above detection). This latter group included liver, rice, canned mushrooms, pork chow mein (classed as pork composite dishes), pecans (classed as other nuts), spinach, prunes, and raisins. Concentrations of Hg in these specific foods were included in this analysis assuming a log-normal distribution with a mean and standard deviation derived from the data of Gunderson (unpublished). The remaining foods with few detected Hg levels were grouped into 11 common categories (see Table 5.10) for easier data manipulation. The Hg concentration data for these 11 latter food groups were assumed to be uniformly distributed between zero and the maximum value reported for any of the individual foods within each group. For all foods other than fish and shellfish, Hg contamination was assumed to be Hg^{2+}.

5.3.11 Commercial fish

Unpublished fish monitoring data were obtained from Fisheries and Oceans Canada (A.Gervais, Fisheries and Oceans Canada, pers. com.). The Hg concentration data for each of commercial finfish and shellfish were defined by log-normal distributions with means of -2.51 ± 1.30 and -4.39 ± 1.15 ln(μg Hg/g tissue wet weight), respectively. For fish and shellfish, all Hg contamination was assumed to be methyl Hg.

5.3.12 Non-commercial fish

Data on the total Hg concentration in a sample of dorsal muscle from 19,628 specimens of lake trout, northern pike and walleye collected since the mid 1970's or later from across Ontario were provided by the OMEE and the Ontario Ministry of Natural Resources (unpublished data). These data were strongly log-normal with a mean total Hg concentration of -0.97 ± 1.27 ln(μg Hg/g tissue wet weight) (range: 0.01-24.0 μg Hg/g tissue wet weight). A probability density function with these characteristics was employed for quantification of the dose of Hg arising from the consumption of non-commercial fish by the general Canadian population.

5.3.13 Absorption of Hg species

Assumptions concerning absorption of Hg^{2+} from the GI tract are described in Section 5.2.6. Assumptions concerning absorption of Hg^{0} from the lung are described in Section 5.2.5. Methyl Hg was assumed to be totally (100%) absorbed when consumed (WHO 1990).

Table 5.10. Summary of Hg contamination data for 140 foods, and their groups.

USFDA food code	HWC food code	description	No. of Detects	Min (ug/g)	Max (ug/g)	General food group
11	9	cottage cheese, 4%	3	0.001	0.001	Dairy
2	2	2% milk	3	0.001	0.002	Dairy
167	5	cream, half & half	6	0.001	0.002	Dairy
164	11	butter, stick type	4	0.001	0.002	Dairy
1	1	whole milk	2	0.002	0.003	Dairy
10	10	cheese, processed	6	0.001	0.003	Dairy
12	8	cheese, cheddar, sharp/mild	5	0.001	0.004	Dairy
9	7	yogurt, sweet, strawberry	5	0.001	0.005	Dairy
8	4	evaporated milk	3	0.001	0.006	Dairy
177	6	ice cream & ice milk	3	0.001	0.023	Dairy

USFDA food code	HWC food code	description	No. of Detects	Min	Max	General food group
4	3	skim milk, fluid	0			Dairy
36	20	eggs, any type	12	0.001	0.012	Eggs
47	166	peanut butter, creamy	6	0.001	0.002	Fats, oils & nuts
160	137	gravy & white sauce (flour,butter,water,milk)	4	0.001	0.008	Fats, Oils & nuts
186	47	pie, pumpkin, frozen	5	0.001	0.001	Fruit & fruit products
103	79	fruit juice, canned	3	0.001	0.001	Fruit & fruit products
80	81	banana, raw	1	0.001	0.001	Fruit & fruit products
101	83	grape juice, canned	2	0.001	0.001	Fruit & fruit products
85	85	pear, raw	2	0.001	0.001	Fruit & fruit products
94	87	cherries, sweet, raw	6	0.001	0.001	Fruit & fruit products
87	155	fruit cocktail, canned in syrup	2	0.001	0.001	Fruit & fruit products
94	157	cherries, canned	6	0.001	0.001	Fruit & fruit products
94	158	cherries, processed	6	0.001	0.001	Fruit & fruit products
185	46	pie, apple, frozen	4	0.001	0.002	Fruit & fruit products

USFDA food code	HWC food code	description	No. of Detects	Min	Max	General food group
92	74	fresh citrus, orange & grapefruit	1	0.002	0.002	Fruit & fruit products
98	76	orange juice	5	0.001	0.002	Fruit & fruit products
100	77	grapefruit juice	4	0.001	0.002	Fruit & fruit products
78	78	apple, red, raw	6	0.001	0.002	Fruit & fruit products
84	80	applesauce, canned	2	0.001	0.002	Fruit & fruit products
83	84	peach, raw	4	0.001	0.002	Fruit & fruit products
86	89	strawberry, raw	5	0.001	0.002	Fruit & fruit products
82	153	peach, canned	2	0.002	0.002	Fruit & fruit products
90	154	pear, canned in heavy syrup	1	0.002	0.002	Fruit & fruit products
86	161	strawberries, canned	5	0.001	0.002	Fruit & fruit products
88	82	grapes, raw (purple/green)	11	0.001	0.003	Fruit & fruit products
79	75	citrus fruit, canned (mandarines)	0			Fruit & fruit products
89	88	cantaloupe, raw	0			Fruit & fruit products
93	91	pinapple, raw	0			Fruit & fruit products
93	165	pineaple, canned in juice	0			Fruit & fruit products

USFDA food code	HWC food code	description	No. of Detects	Min	Max	General food group
27	21	liver, beef/calf, cooked	27	0.001	0.005	Liver
17	23	luncheon meats canned	5	0.001	0.001	Meat
28	110	frankfurters, cooked	7	0.001	0.001	Meat
17	135	luncheon meat, ham	5	0.001	0.001	Meat
28	169	wieners, canned	7	0.001	0.001	Meat
16	12	beef, loin/sirloin, cooked	4	0.001	0.002	Meat
20	16	ham, or bacon, cooked	8	0.001	0.002	Meat
23	17	beef, veal cuttlet, cooked	6	0.002	0.002	Meat
22	18	lamb chop, cooked	7	0.001	0.002	Meat
16	122	beef steak, lean only	4	0.001	0.002	Meat
19	129	pork sausage, cooked	7	0.001	0.002	Meat
22	130	lamb, separable, lean only	7	0.001	0.002	Meat
14	13	beef, roasted and stewed	5	0.001	0.003	Meat
21	15	pork chops and roast, cooked	3	0.001	0.003	Meat

USFDA food code	HWC food code	description	No. of Detects	Min	Max	General food group
14	123	beef roast & stew	5	0.001	0.003	Meat
21	127	pork, fresh lean only	3	0.001	0.003	Meat
147	14	beef hamburger	7	0.001	0.004	Meat
30	22	bologna and salami	3	0.001	0.006	Meat
130	72	mushrooms, raw & canned	37	0.005	0.08	Mushrooms
191	104	soda, cola/lemon lime, sweetened, can	3	0.001	0.001	Other beverages
199	105	wine, 12.2% alcohol	1	0.001	0.001	Other beverages
194	171	soda, atrificial sweetener, cola	1	0.001	0.001	Other beverages
200	121	whiskey, 80 proof	1	0.002	0.002	Other beverages
189	175	soft drink powder, chocolate & cherry	5	0.001	0.002	Other beverages
198	106	beer, canned	3	0.001	0.003	Other beverages
49	167	pecans (nuts and seeds, other)	25	0.001	0.003	Other nuts (pecans)
91	156	plums, canned	3	0.001	0.001	Plums & prunes
96	86	prunes & plums, raw, purple	26	0.001	0.003	Plums & prunes
153	128	pork composite dishes	27	0.001	0.006	Pork Composite

USFDA food code	HWC food code	description	No. of Detects	Min	Max	General food group
						dishes
150	132	poultry, chicken composite dishes	6	0.001	0.002	Poultry
25	131	poultry, no skin, not fried	14	0.001	0.005	Poultry
26	19	poultry, chicken & turkey, whole or part	14	0.001	0.011	Poultry
95	109	raisins, dried	29	0.001	0.005	Raisins
50	45	rice, white, cooked	24	0.001	0.004	Rice
75	140	cereal, krisped rice	31	0.001	0.008	Rice
148	124	beef, composite dishes	7	0.001	0.001	Soup & Mixed dishes
144	48	pizza, cheese, cooked	8	0.001	0.002	Soup & mixed dishes
157	28	soups, all excluding tomatoe	6	0.001	0.006	Soup & mixed dishes
156	30	soup, cream of tomato	5	0.001	0.006	Soup & mixed dishes
106	145	spinach	28	0.001	0.011	Spinach
146	49	macaroni and cheese	4	0.001	0.001	Staples
63	35	flour, wheat all purpose	8	0.001	0.002	Staples
184	37	cookies, choc. chip & sandwich type	9	0.001	0.002	Staples

USFDA food code	HWC food code	description	No. of Detects	Min	Max	General food group
69	50	noodles, egg, cooked	4	0.001	0.002	Staples
137	53	potatoes, baked	7	0.001	0.002	Staples
135	55	mashed potatoes	3	0.001	0.002	Staples
65	107	muffins, blueberry/plain	7	0.001	0.002	Staples
151	141	pasta, spaghetti & lasagna	8	0.001	0.002	Staples
62	33	bread, whole wheat	5	0.001	0.003	Staples
182	38	donuts & danish pastry/ sweet roll	8	0.001	0.003	Staples
66	39	crackers, saltine	5	0.001	0.003	Staples
68	40	pancakes	8	0.001	0.003	Staples
71	43	cornflakes	6	0.001	0.003	Staples
134	56	french fries, cooked	4	0.001	0.003	Staples
76	139	cereal, granola, plain	12	0.001	0.003	Staples
59	34	rolls, white, soft	6	0.001	0.004	Staples
51	42	rolled oats, cooked	4	0.002	0.004	Staples

USFDA food code	HWC food code	description	No. of Detects	Min	Max	General food group
138	57	potato chips	10	0.001	0.004	Staples
43	108	navy beans, boiled	3	0.001	0.004	Staples
58	32	bread, white enriched	4	0.001	0.005	Staples
180	36	cake, fresh or frozen	9	0.001	0.005	Staples
74	44	cereal, raisin bran	18	0.001	0.005	Staples
41	168	lima beans mature, bioled	8	0.001	0.007	Staples
52	41	farina, enriched, cooked	0			Staples
171	97	jelly, grape	1	0.001	0.001	Sugar & sweets
175	99	pudding, instant chocolate	2	0.001	0.001	Sugar & sweets
187	100	candy, milk chocolate	2	0.001	0.001	Sugar & sweets
188	101	candy, caramels	5	0.001	0.001	Sugar & sweets
190	111	gelatin, strawberry	4	0.001	0.001	Sugar & sweets
170	96	syrup, pancake syrup, bottled	3	0.001	0.002	Sugar & sweets
172	98	honey	8	0.001	0.002	Sugar & sweets
169	95	sugar, white	4	0.001	0.003	Sugar & sweets

USFDA food code	HWC food code	description	No. of Detects	Min	Max	General food group
127	66	carrots, raw	6	0.001	0.001	Vegetables
119	71	tomato sauce	1	0.001	0.001	Vegetables
122	146	green beans, canned	1	0.001	0.001	Vegetables
54	51	corn, boiled	5	0.001	0.002	Vegetables
114	59	celery, raw	6	0.001	0.002	Vegetables
128	67	onions	7	0.001	0.002	Vegetables
118	70	tomato juice, canned	3	0.001	0.002	Vegetables
115	143	asparagus, boiled	7	0.001	0.002	Vegetables
129	148	vegetables, mixed, canned	3	0.001	0.002	Vegetables
173	149	catsup	7	0.001	0.002	Vegetables
55	178	corn, canned	4	0.001	0.002	Vegetables
112	58	sauerkraut, canned	5	0.001	0.003	Vegetables
46	65	peas, green, boiled	4	0.001	0.003	Vegetables
163	92	vegetable oils & salad dressings	8	0.001	0.003	Vegetables

USFDA food code	HWC food code	description	No. of Detects	Min	Max	General food group
162	93	margarine, stick type	5	0.001	0.003	Vegetables
113	63	broccoli, boiled	6	0.001	0.004	Vegetables
48	94	peanuts, dry roasted	8	0.001	0.004	Vegetables
126	152	squash, winter, boiled	7	0.001	0.004	Vegetables
109	61	lettuce, raw	7	0.001	0.005	Vegetables
123	73	cucumber, raw	1	0.005	0.005	Vegetables
131	112	beets, raw	4	0.001	0.005	Vegetables
161	151	pickles, dill	11	0.001	0.005	Vegetables
131	170	beets, canned	4	0.001	0.005	Vegetables
57	179	popcorn, popped	7	0.001	0.006	vegetables
121	64	green beans, boiled	6	0.001	0.008	Vegetables
125	60	green pepper, sweet, raw	3	0.001	0.009	Vegetables
117	69	tomato, raw	3	0.001	0.01	Vegetables
45	147	peas, green, canned	3	0.009	0.013	Vegetables
116	62	cauliflower, boiled	6	0.001	0.021	Vegetables

5.3.14 Time spent indoors

Canadians spend an average of 22 hours per day indoors (Statistics Canada, 1991). Neither the raw data nor other characteristics of these data (standard deviation, skewness, kurtosis, etc.) were available. Therefore, time spent indoors was defined by a triangular distribution with a minimum of 8 hours/day, and most likely value of 22 hours/day and a maximum of 24 hours/day. Time outdoors was subsequently derived as the difference between time spent indoors and 24 hours.

5.3.15 Sensitivity analysis

A sensitivity analysis was conducted using methods described by Decissioneering (1993) in order to evaluate the relative influence of the different model variables to overall variance is estimates of exposure.

5.3.16 Results

Ranges of estimated total exposure from all sources, and corresponding probabilities for toddlers, children, teens, adults and seniors, are illustrated in Figures 5.21 through 5.25. For amalgam alone, these estimated exposures and probabilities are presented in Figures 5.26 through 5.30. As in Section 5.2, the distributions are positively skewed indicating that most people will experience exposure toward the lower end of the indicated ranges.

Table 5.11 summarizes the results of the assessment of total exposure for each age group while exposure from amalgam only is summarized in Table 5.12. The mean total exposure (from all sources) for adults was estimated to be 9.4 μg/day, while the average exposure specifically from amalgam was estimated to be 3.4 μg/day. On a per kg body weight (bw) basis, estimates of total Hg exposure were: toddler 0.19 μg/kg bw/day; child 0.22 μg/kg bw/day; teen 0.12 μg/kg bw/day; adult 0.14 μg/kg bw/day; 0.10 senior μg/kg bw/day. Estimates of exposure from amalgam only, on a per kg body weight basis were: toddler 0.04 μg/kg bw/day; child 0.04 μg/kg bw/day; teen 0.03 μg/kg bw/day; adult 0.05 μg/kg bw/day; senior 0.03 μg/kg bw/day. Estimates of exposure from fixed numbers of fillings, on a per kg body weight basis, are presented in Table 5.13.

As a source of Hg, amalgam represented, on average, 50% of total exposure for adults, but less so for other age groups. For other age groups, the average proportion of total Hg exposure estimated to arise from amalgam ranged from 33% (child) to 42% (senior) (see Table 5.14).

The ten most significant variables influencing adult exposure are presented in Figure 5.31. As with the previous method of exposure assessment (Section 5.2), the most significant parameter influencing total adult exposure was the number of amalgam fillings. Also included in the top ten factors were the various assumptions necessary to estimate the dose of Hg from the number of amalgam fillings. The rate of consumption of commercial (saltwater) fish and the Hg concentration in these fish were also relatively significant to total exposure estimation, as would be expected.

Table 5.11. Results for total Hg exposure from Assessment II (after Richardson et al. 1995).

Statistic		Toddler (µg/day)	Child (µg/day)	Teen (µg/day)	Adult (µg/day)	Senior (µg/day)
Mean		3.28	5.56	6.72	9.44	6.79
Median (approx.)		2.09	3.57	3.97	6.04	5.90
Mode (approx.)		2.38	8.74	9.07	14.13	15.28
Standard Deviation		10.98	33.17	30.73	42.93	40.64
Percentiles:	5%	0.51	0.85	0.85	1.05	0.98
	10%	0.69	1.15	1.20	1.61	1.53
	20%	1.05	1.76	1.89	2.71	2.62
	30%	1.41	2.36	2.58	3.82	3.72
	40%	1.76	2.97	3.28	4.93	4.81
	50%	2.09	3.57	3.97	6.04	5.90
	60%	2.41	4.18	4.66	7.14	7.00
	70%	2.74	4.78	5.36	8.25	8.09
	80%	3.06	5.39	6.05	9.36	9.18
	90%	4.20	5.99	10.06	15.78	10.28
	95%	5.64	10.36	14.90	22.97	18.96

Table 5.12. Results for exposure from amalgam only, from Assessment II.

Statistic		Toddler (µg/day)	Child (µg/day)	Teen (µg/day)	Adult (µg/day)	Senior (µg/day)
Mean		0.79	1.10	1.91	3.38	2.08
Median (approx.)		0.59	0.71	1.07	1.90	0.90
Mode (approx.)		0.29	0.22	0.20	0.36	0.26
Standard Deviation		0.73	1.17	2.50	4.23	3.17
Percentiles:	5%	0.14	0.13	0.15	0.15	0.10
	10%	0.19	0.18	0.22	0.28	0.17
	20%	0.29	0.27	0.38	0.54	0.28
	30%	0.38	0.39	0.58	0.90	0.42
	40%	0.48	0.54	0.80	1.34	0.62
	50%	0.59	0.71	1.07	1.90	0.90
	60%	0.72	0.94	1.45	2.66	1.33
	70%	0.89	1.24	2.00	3.72	1.99
	80%	1.13	1.67	2.83	5.37	3.08
	90%	1.56	2.51	4.44	8.43	5.37
	95%	2.12	3.41	6.52	11.55	7.85

Table 5.13. Estimates of average Hg exposure (µg Hg/kg bw/day) for fixed numbers of fillings, by age group.

Age group	Number of fillings					
	1	2	4	8	12	20
Toddler	0.011	0.024	0.053	0.131	--[a]	--[a]
Child	0.008	0.016	0.036	0.089	0.168	--[a]
Teen	0.004	0.007	0.016	0.040	0.076	0.210
Adult	0.003	0.006	0.014	0.034	0.064	0.177
Senior	0.003	0.006	0.014	0.034	0.065	0.179

a - age group unlikely to have this number of filled teeth.

Table 5.14. Percent of total Hg exposure arising from amalgam.

Statistic		Toddler (%)	Child (%)	Teen (%)	Adult (%)	Senior (%)
Mean		34	32	40	50	42
Median (approx.)		32	29	38	52	39
Mode (approx.)		23	17	14	84	12
Standard Deviation		19	21	25	28	27
Percentiles:	5%	6	5	5	5	4
	10%	10	7	9	10	9
	20%	16	12	15	20	15
	30%	21	17	22	31	22
	40%	27	23	30	42	30
	50%	32	29	38	52	39
	60%	38	36	46	62	50
	70%	44	44	55	71	60
	80%	52	52	65	78	71
	90%	62	64	76	86	82
	95%	69	72	82	90	88

Figure 5.21. Distribution of estimated total Hg exposure (µg/day) for toddlers.

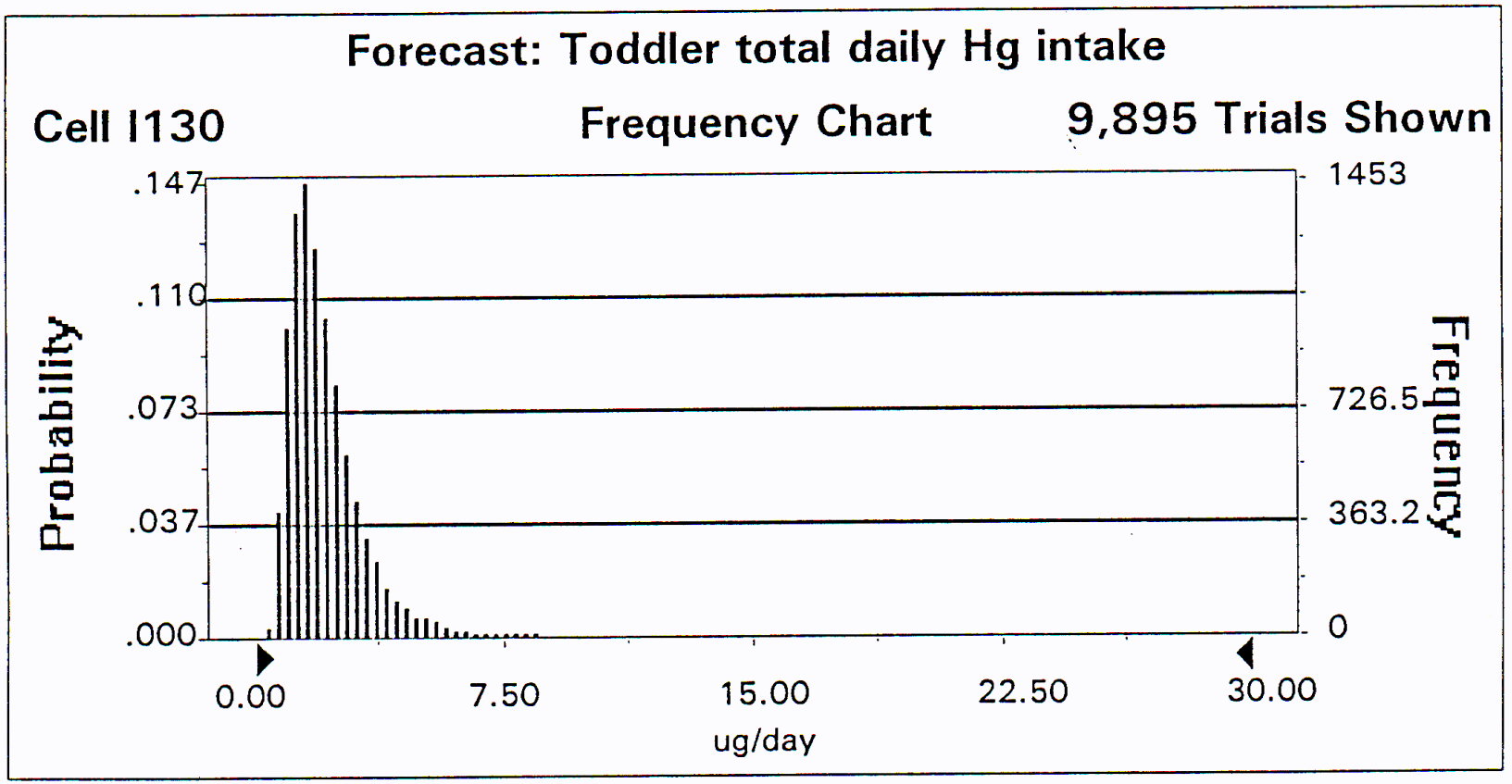


Figure 5.22. Distribution of estimated total Hg exposure (µg/day) for children.

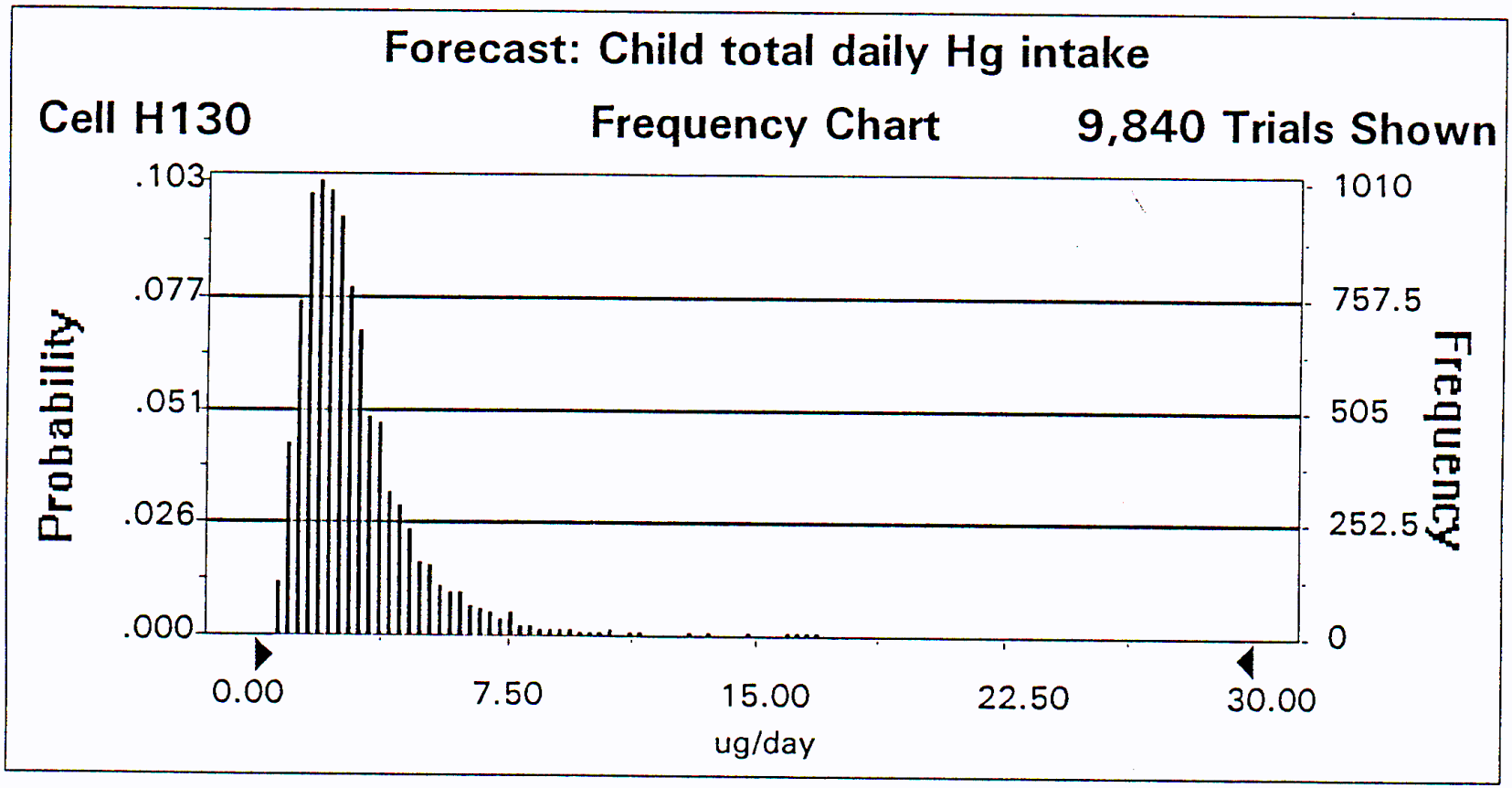


Figure 5.23. Distribution of estimated total Hg exposure (µg/day) for teens.

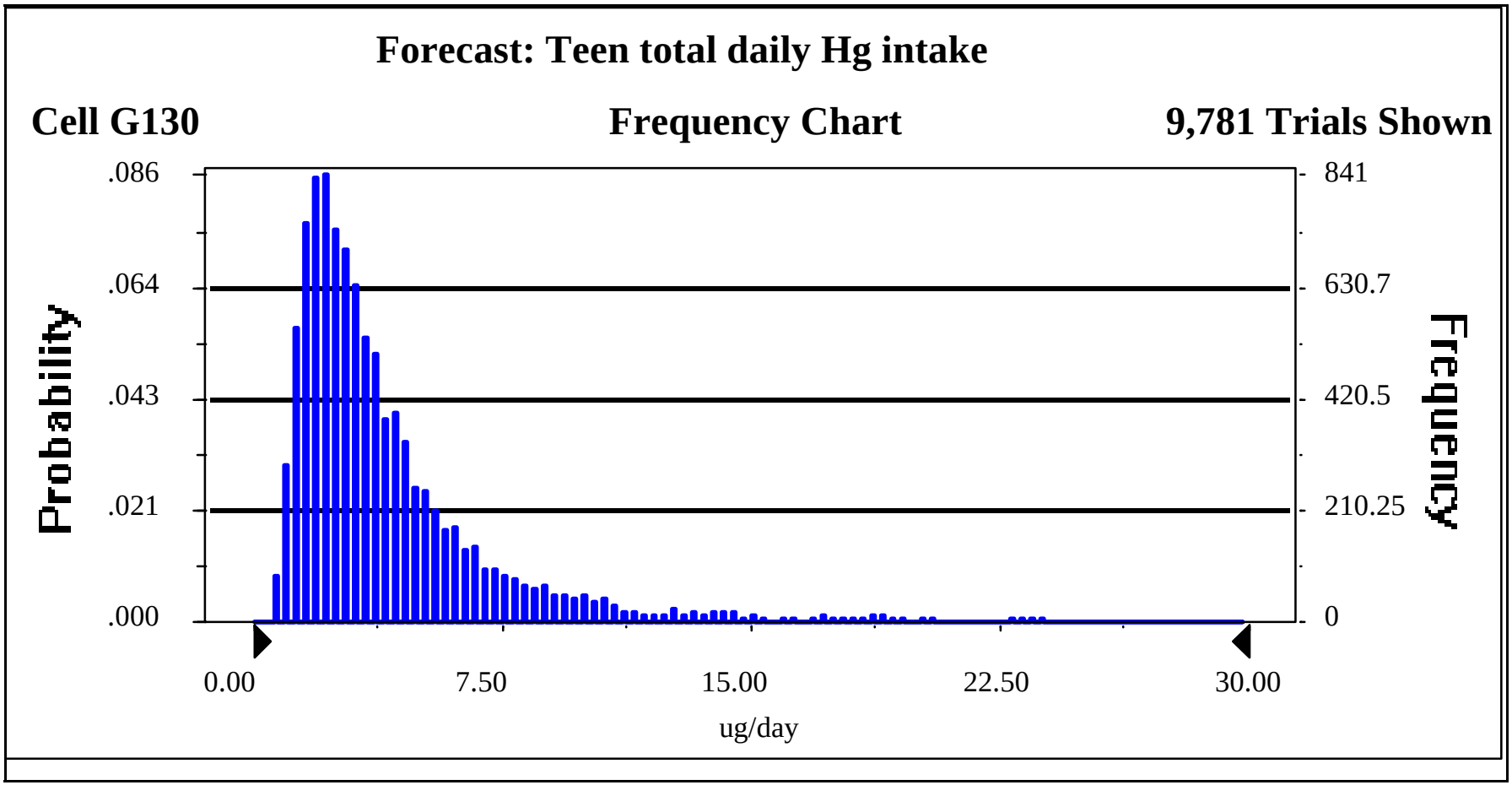


Figure 5.24. Distribution of estimated total Hg exposure (µg/day) for adults.

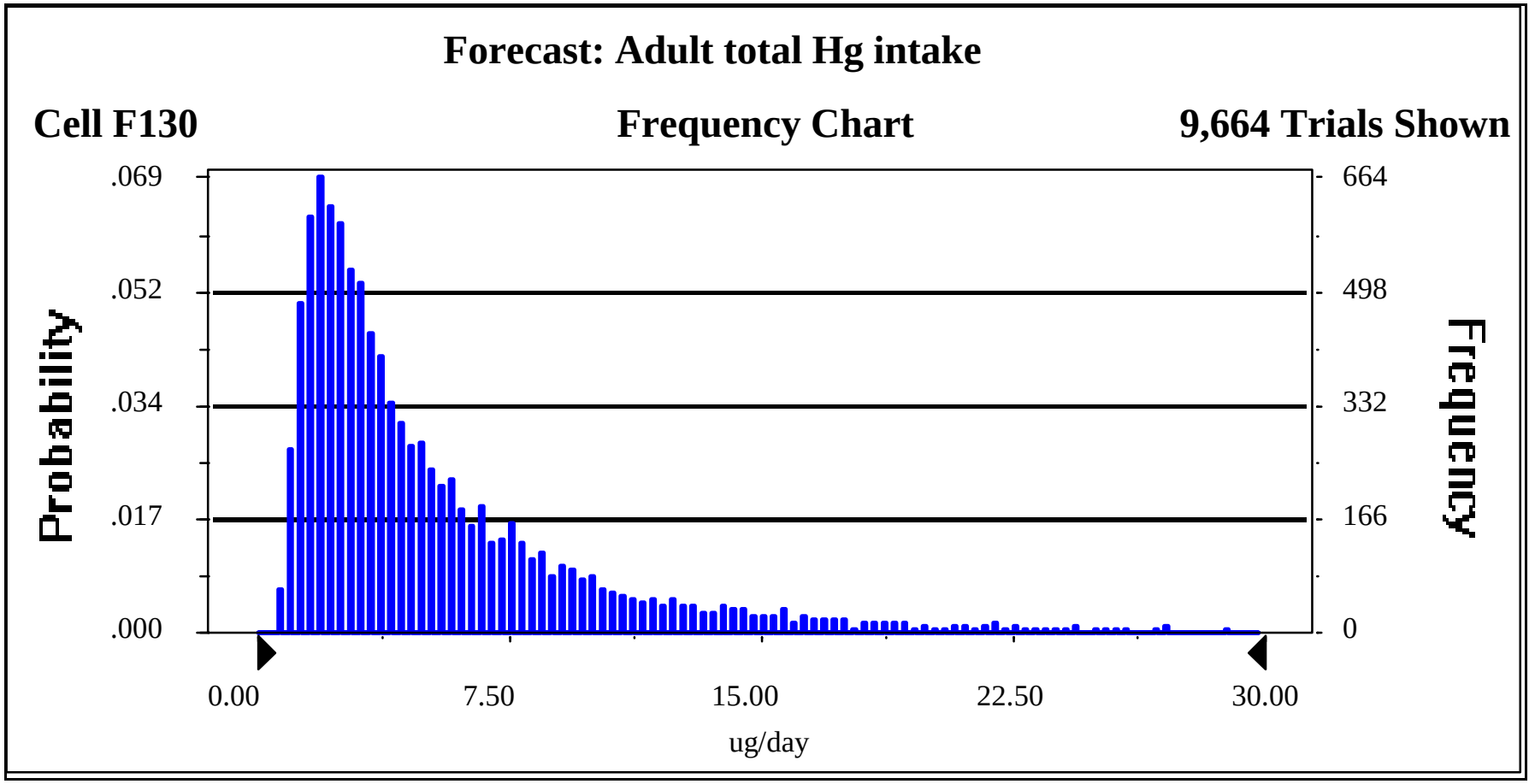


Figure 5.25. Distribution of estimated total Hg exposure (µg/day) for seniors.

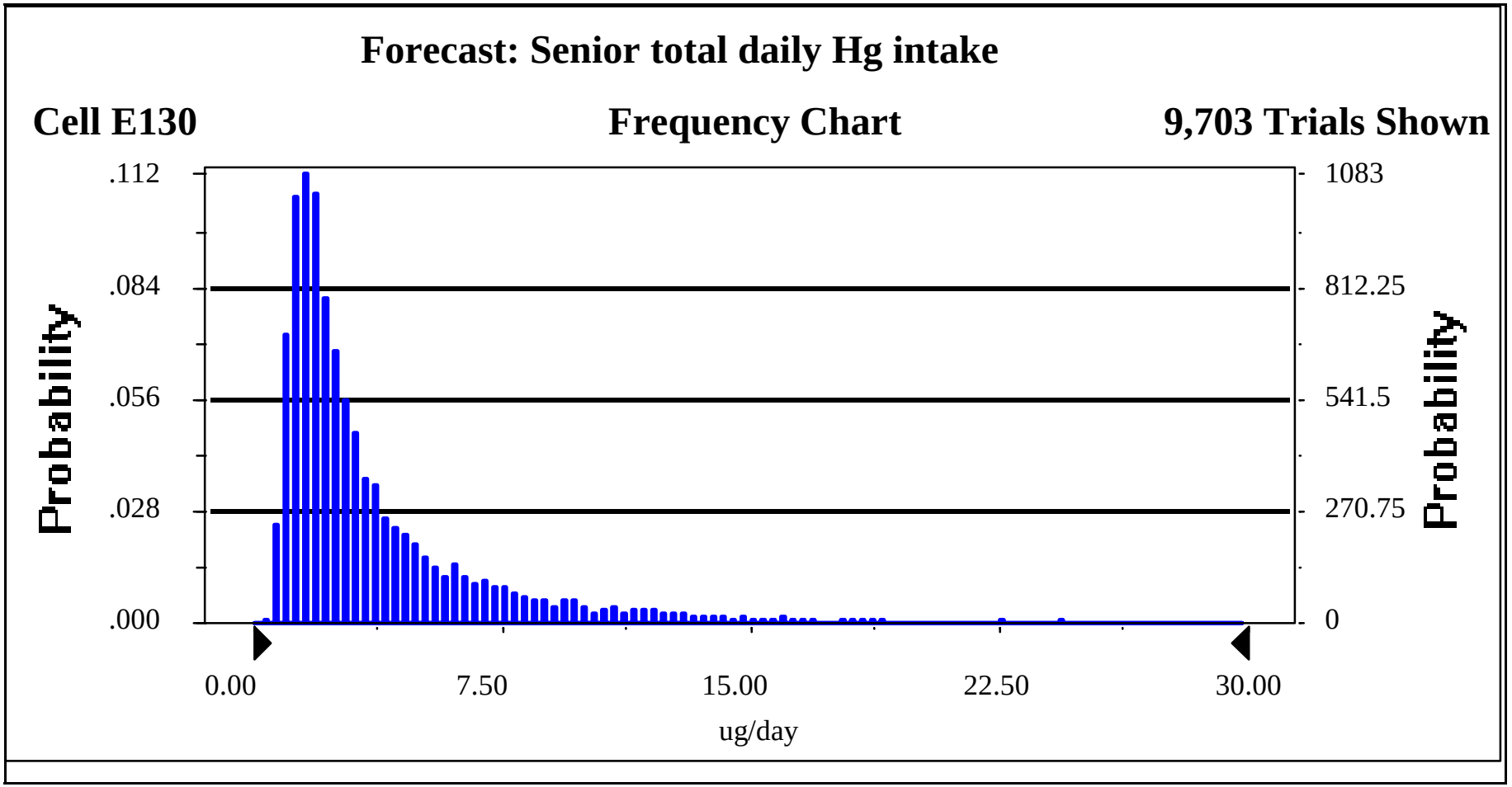


Figure 5.26. Distribution of estimated Hg exposure (µg/day) for toddlers from amalgam fillings only.

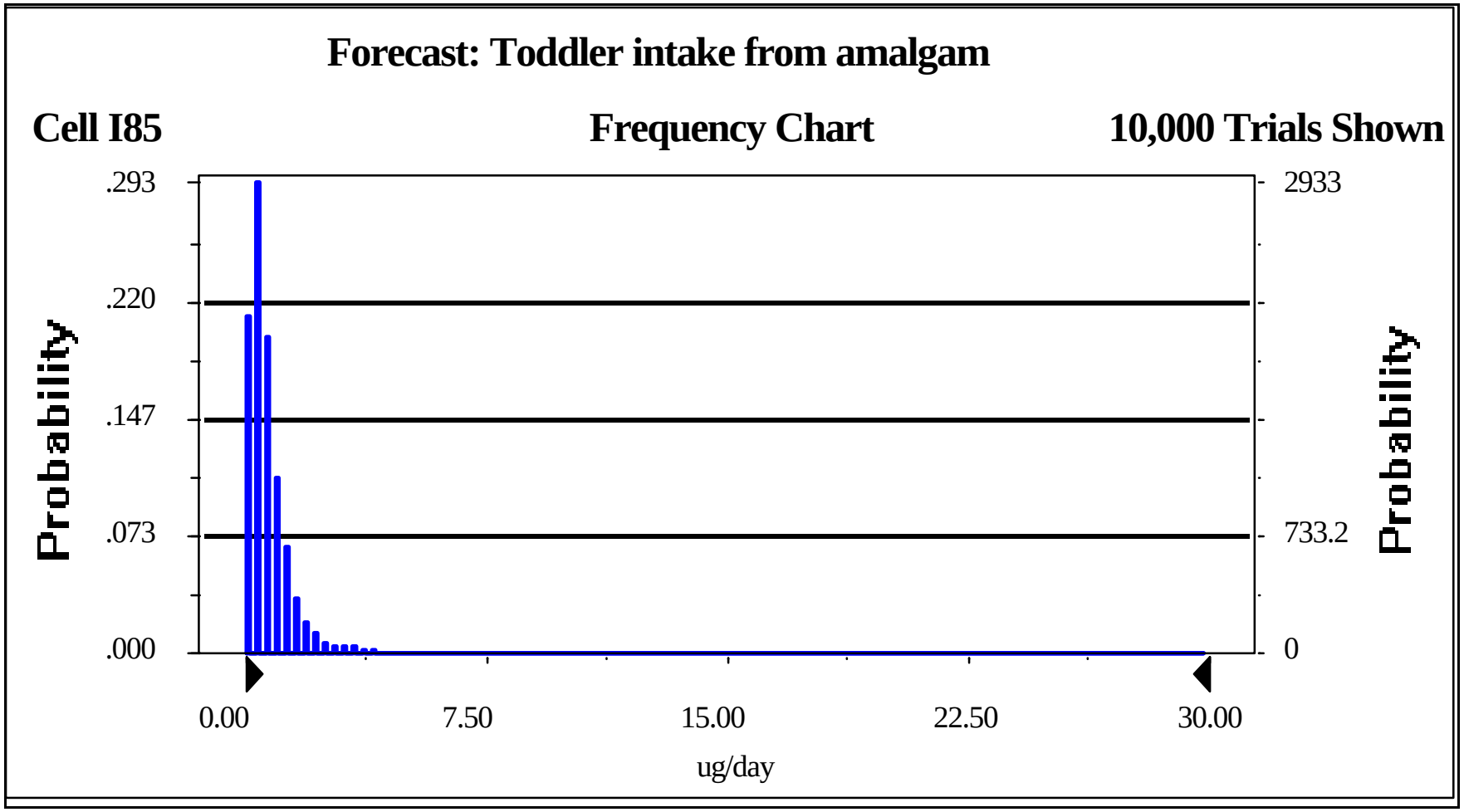


Figure 5.27. Distribution of estimated Hg exposure (µg/day) for children from amalgam fillings only.

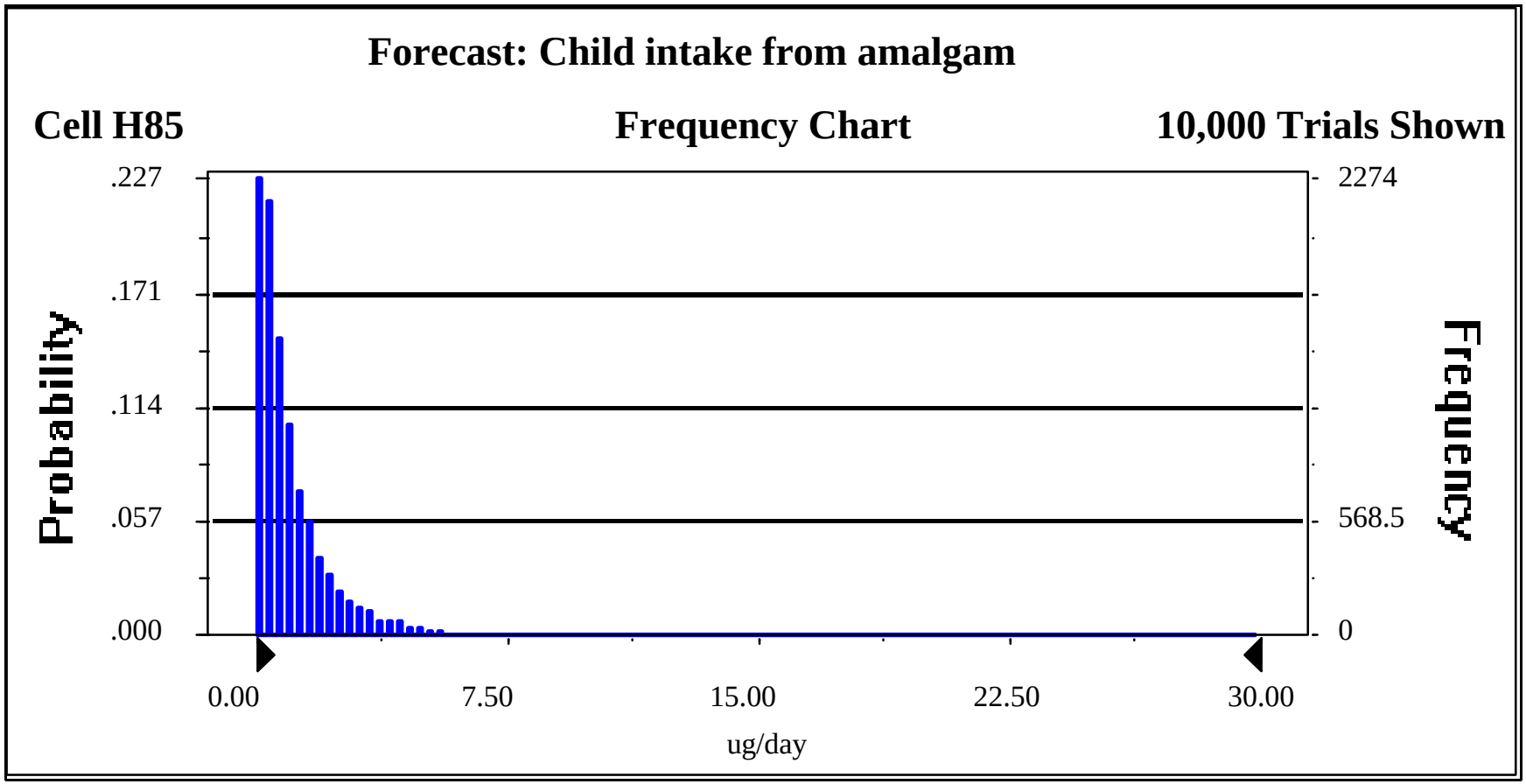


Figure 5.28. Distribution of estimated Hg exposure (µg/day) for teens from amalgam fillings only.

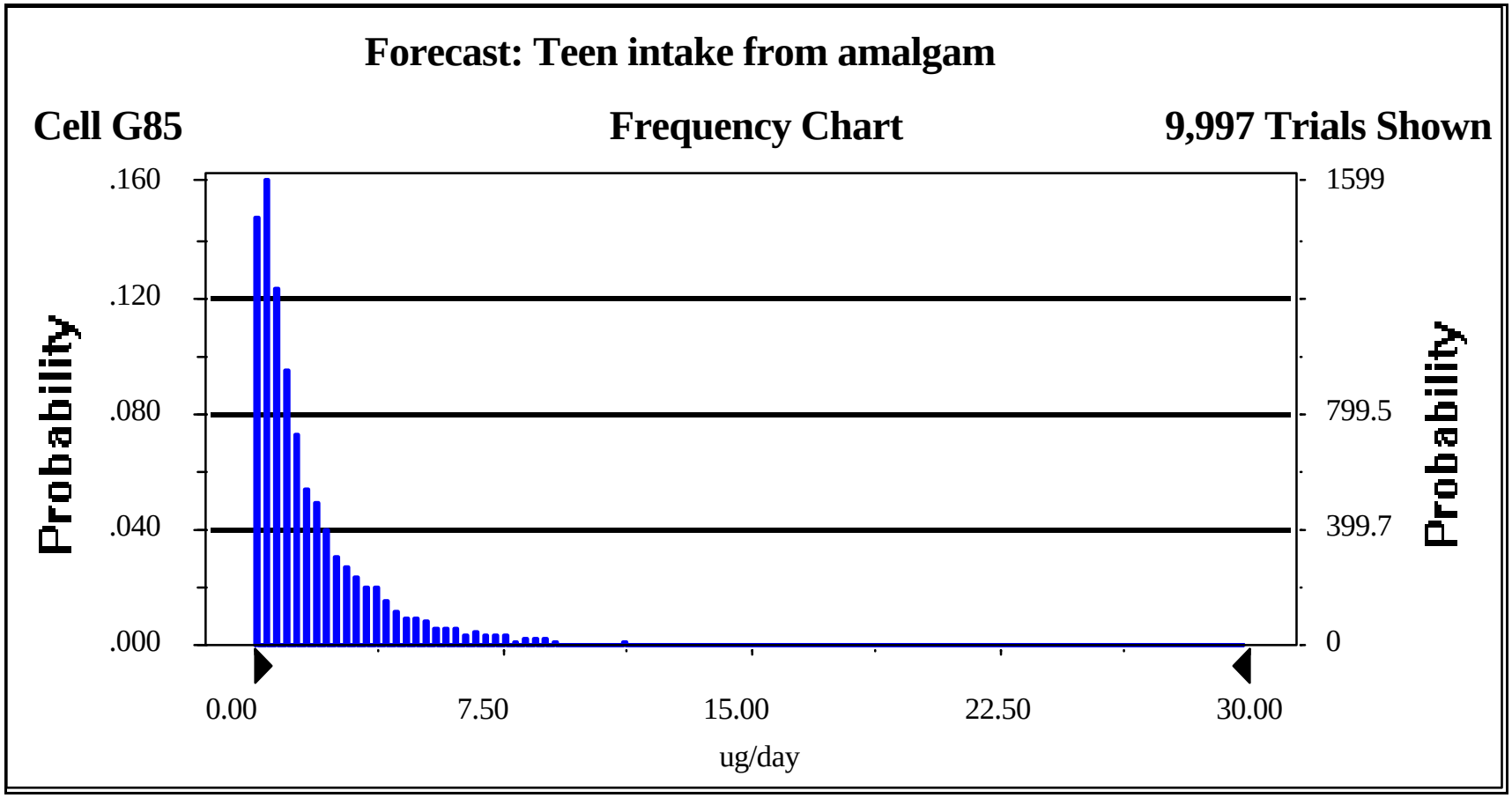


Figure 5.29. Distribution of estimated Hg exposure (µg/day) for adults from amalgam fillings only.

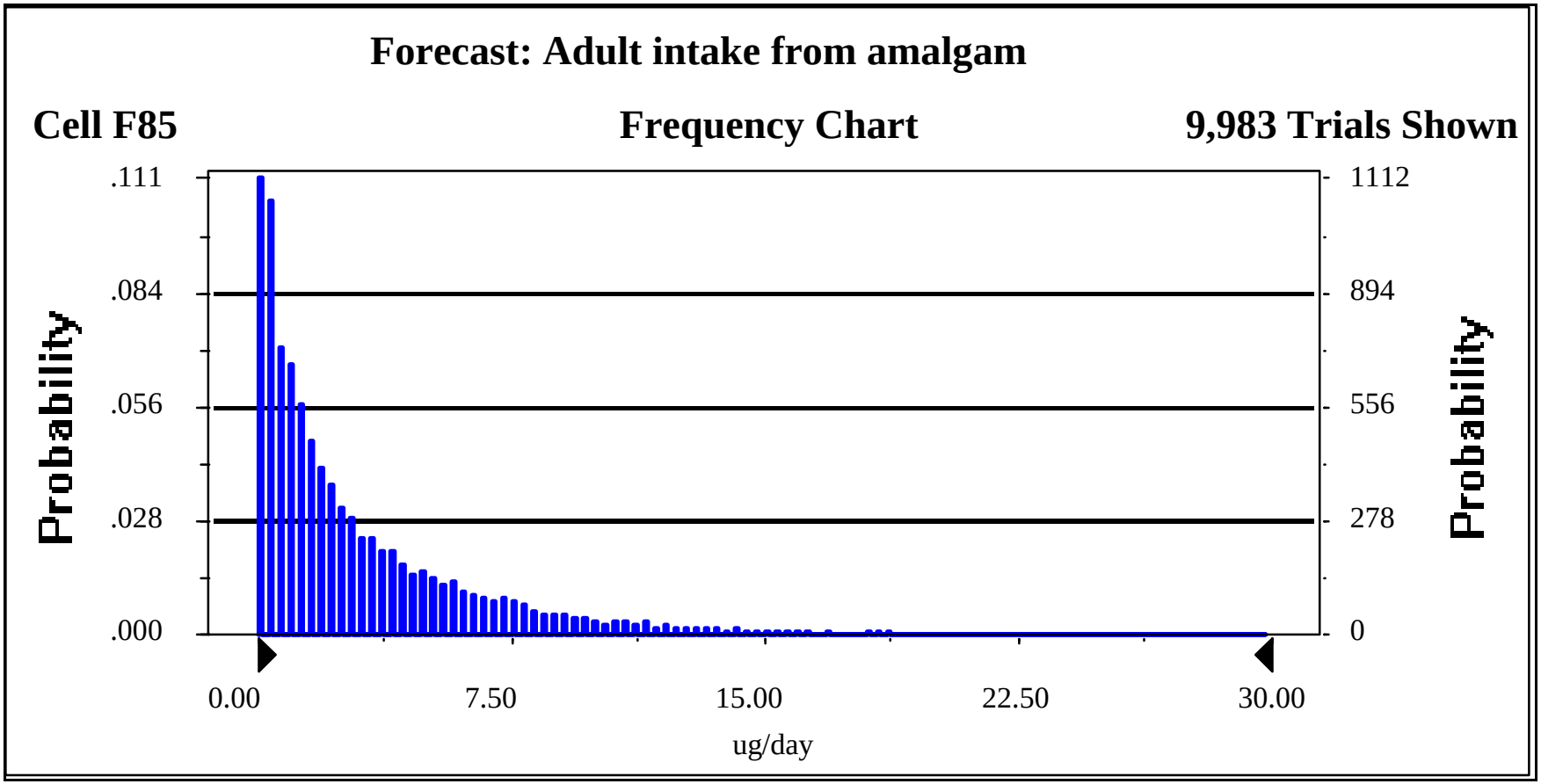


Figure 5.30. Distribution of estimated Hg exposure (µg/day) for seniors from amalgam fillings only.

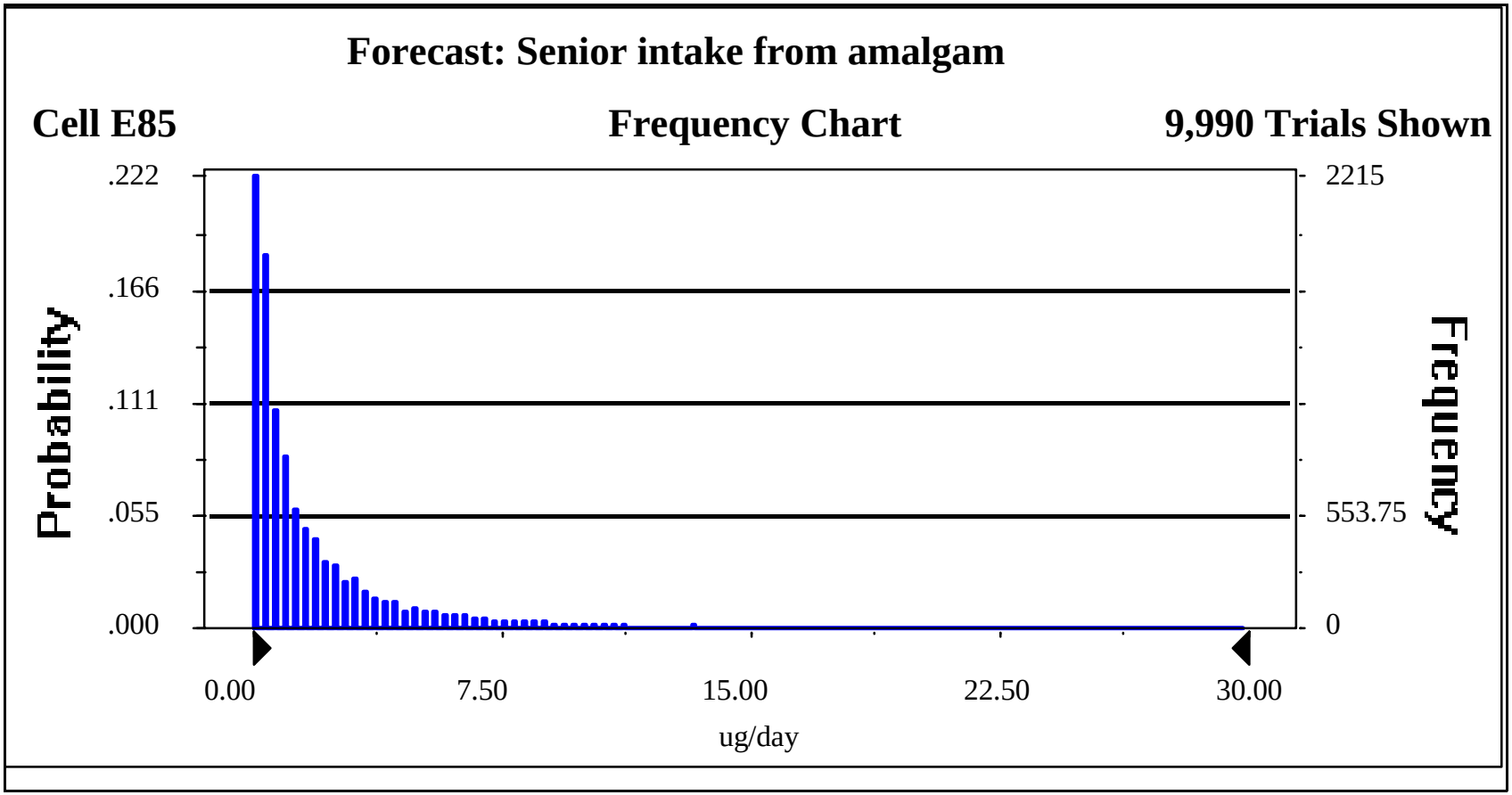
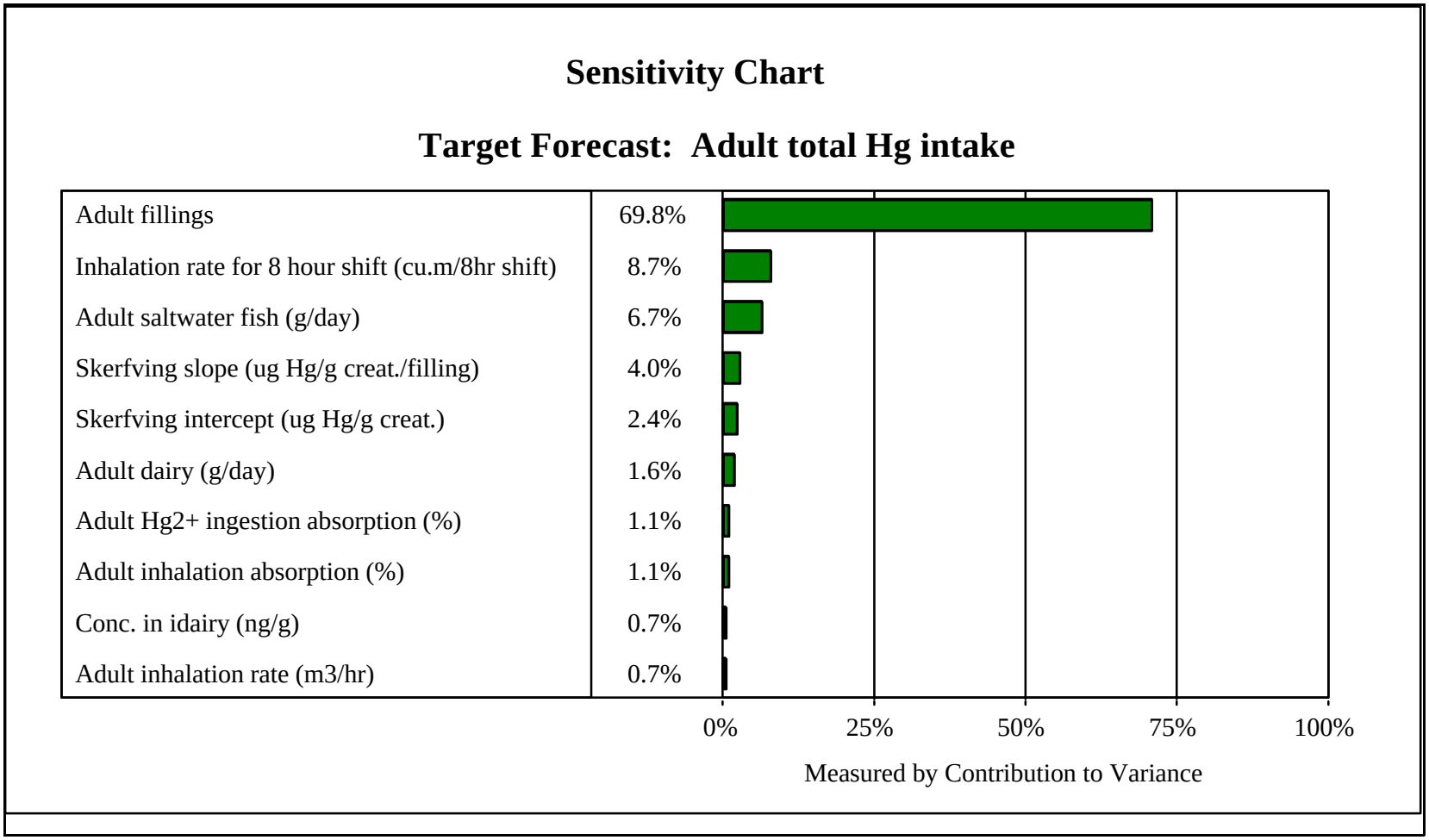


Figure 5.31. Sensitivity analysis for adult exposure. Parameters listed are the 10 most significant factors influencing estimated exposure.



6.0 Uptake, Tissue Distribution, Metabolism and Excretion

An overview of Hg vapour metabolism is provided by Lorscheider *et al.* (1995), while the pharmacokinetics of Hg have been reviewed in detail by ATSDR (1994) and WHO (1990, 1991). Exposure to Hg^0 is predominantly via the lung, with reported absorption ranging from 61 to 86% (Neilsen-Kudsk 1965; Teisinger and Fiserova-Bergerova 1965; Hursh et al. 1976; Oikawa et al. 1982) The ratio of plasma:erythrocyte Hg concentrations is approximately 1 or 2 for Hg^0 (WHO 1991), compared to 0.05 for methylHg (WHO 1990). WHO (1991) concluded from *in vitro* studies of Hg oxidation in blood (Hursh et al. 1988) that transport from the lung to the blood-brain barrier is direct and rapid with little oxidation (<10%) of Hg^0 to Hg^{2+} before reaching the blood-brain barrier. A portion of Hg^0 crosses the blood-brain barrier where it is subsequently oxidized to Hg^{2+}. Hg^{2+} can not readily cross the blood-brain barrier and is thereby 'trapped' in the brain or CNS (Lorscheider et al. 1995). A greater proportion of Hg^0 absorbed via the lung is deposited in the brain than for other routes of exposure and forms of Hg (WHO 1991). The primary organ of deposition is the kidney, with lesser amounts in the liver, CNS and other tissues (WHO 1991).

Intestinal absorption of ingested Hg^{2+} or amalgam particles is low although quantitative data are limited. Elinder et al. (1988) estimated <1% of metallic Hg and <10% of Hg^{2+} is absorbed from the gut. WHO (1976) estimated a gastrointestinal absorption rate of 7% for Hg^{2+}. Animal studies indicate that gastrointestinal absorption of these forms of Hg is greater in neonates than older animals (Kostial et al. 1978), and may also be influenced by diet (Kostial et al. 1978).

In vitro studies have demonstrated that oral and intestinal microflora can methylate Hg^{2+} (Rowland *et al.* 1975; Heintze *et al.* 1983). However, it is unclear to what extent this transformation takes place *in vivo*.

Excretion of Hg following exposure to Hg vapour is predominantly via urine and faeces, although a small proportion of excretion may also occur via expired air, saliva, sweat and breast milk (WHO 1991). Urinary excretion appears to predominate for high (occupational) exposure (WHO 1991). Skare and Engqvist (1994) reported up to 10 fold greater excretion of Hg via faeces than via urine over a 24 hour period, for a group of subjects with amalgam fillings. However, it is unclear what proportion of this Hg in the faeces represented systemically-absorbed and excreted Hg versus particulate and inorganic Hg passing through the gastrointestinal tract. The low rates of absorption from the gut imply that a significant portion of this Hg had passed directly through the G.I. tract. Despite the large quantity of Hg excreted in faeces, urine Hg concentration was a better predictor of absorbed dose from amalgam than faecal Hg levels (from Skare and Engqvist, 1994: urine [Hg] = -1.79 + 0.18*(no. of amalgam surfaces), $r=+0.81$, $p<0.004$, $n=10$; faecal [Hg] = 14.46 + 1.48*(no. of amalgam surfaces), $r=+0.61$, $p<0.04$, $n=10$).

Hg elimination from the head has a reported half-life of about 20 days (Hursh *et al.* 1976). However, there is some evidence that the half-life in the brain may be longer than that in the rest of the body (US EPA 1985; Piotrowski and Inskip 1981). Modelling of Hg accumulation and elimination in the brain suggests that a small elimination phase may exist, having a half life approaching 30 years (Bernard and Purdue, 1984).

Hg vapour is ultimately converted to Hg^{2+} in the body (Lorscheider *et al.* 1995) and its whole body elimination is, therefore, the same as that for Hg^{2+}. Using whole body measurements, Skerfving

and Vostal (1972) found that the elimination of mercuric salts in human subjects had a biological half-life of 30 to 60 days. No sex difference in body burden was noted. The half lives of other forms of Hg in humans are similar (WHO 1991). The biological half-life of methyl Hg, determined by human experiments using a single exposure, was roughly 50 days; measurement in which a long-term exposure was interrupted indicated a half-life of roughly 70 days; in both cases there was a large spread in values (WHO 1990).

7.0 Toxicology

The toxicity of Hg (all forms) via ingestion and dermal absorption, and the acute and subchronic toxicity of Hg vapour exposure via inhalation, have been extensively reviewed by ATSDR (1994) and WHO (1990, 1991). As exposure to Hg from amalgam is predominantly via inhalation and is a low level, chronic phenomenon, the toxicity of methyl Hg and mercuric salts, and the acute and subchronic toxicity of Hg vapour, will not be discussed here.

7.1 Carcinogenicity/mutagenicity

The potential carcinogenicity of Hg has been extensively reviewed by the International Agency for Research on Cancer (IARC 1993) and by Boffetta *et al.* (1993). IARC (1993) concluded that metallic Hg and inorganic Hg compounds were not classifiable as to their carcinogenicity to humans (IARC Group 3). Confounding exposures to other potential carcinogens such as arsenic or radiation, no demonstrable dose-response associations in the limited data available, and no consistent types or sites of cancers, suggest that Hg vapour is not likely an occupational carcinogen. However, better epidemiologic and experimental evidence are needed to confirm that Hg is not an occupational carcinogen (Boffetta *et al.* 1993).

In the only study that examined the association between cancer incidence and the presence of amalgam dental fillings, Ryan *et al.* (1992) reported a significantly decreased risk of glioma (tumour of the supporting structure of nervous tissue) (sex and age-adjusted relative risk = 0.47; 95% confidence limits 0.25 to 0.91), although no linear trend with number of amalgams was evident.

From these reviews and studies, it was concluded that carcinogenicity is not a probable hazard associated with amalgam, or with the low level of Hg exposure associated with dental fillings.

7.2 Teratogenicity/reproductive toxicology

Most available information on the teratogenic and reproductive toxicity of Hg has been reviewed by WHO (1990, 1991) and ATSDR (1994). There is no evidence to suggest that any disruption of fertility or reproduction will occur at levels of Hg exposure associated with amalgam fillings. Cordier *et al.* (1991) reported an increased risk of spontaneous abortion in women who's husbands had urine Hg concentrations in excess of 50 µg/L. This is 5 to 10 times the urine concentration found in non-occupationally exposed persons with >20 amalgam fillings (Skerfving, 1991). In a survey of fertility in 418 female dental assistants, 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 (defined as placing less than 30 amalgams per week). However, fertility in a subset with higher Hg exposure (30 or more amalgams placed per week and 4 or more poor Hg hygiene factors) was reportedly reduced to 63% that of controls. Data related specifically to dental amalgam were not located, however it is not anticipated that the low level of exposure arising from amalgam will adversely affect fertility or reproduction.

The teratogenicity of methylHg is well known (WHO 1990). However, much less information is available related to Hg vapour (reviewed by WHO (1991), Goering et al. (1992) and ATSDR (1994)). Drasch *et al.* (1994) found an association between maternal amalgam load and levels of Hg in various fetal and neonate tissues (excluding brain tissue). No gross histopathological abnormalities were observed in the tissues examined (Hildebrandt, Bundesinstitut fur Arzneimittel und Medizinprodukte, Germany, pers. com.).

No studies of neurological development of children associated with maternal Hg vapour exposure were located. In a study involving rats, Danielsson *et al.* (1993) reported a reduced performance in the radial arm maze, reduced ability to adapt to a novel environment, and altered motor activity at certain stages of development in rats exposed *in utero* following maternal exposure to Hg vapour, at both high and low levels of exposure. Impairment was greater for the high maternal Hg vapour exposure (200 μg Hg/m^3) than for the low maternal exposure (70 μg Hg/m^3). Most measures of developmental maturation showed no significant difference from controls. Levels of Hg in the brains of rats who's mothers were exposed to the low Hg vapour level were not significantly different from the controls, but levels in the liver and kidney were significantly higher. Elevated levels in kidney and liver, but not in CNS tissue, was also observed by Drasch *et al.* (1994) in their study of tissue Hg levels in deceased neonates and young children of mothers with amalgam fillings.

The overall implications of low level prenatal Hg exposure for neuropsychological development are unknown at this time.

7.3 Nephrotoxicity

Nephrotoxicity has been thoroughly reviewed by ATSDR (1994). The kidney is the primary site of Hg accumulation in the body following exposure to Hg in any form, via any route (WHO 1991). However, aside from possible auto-immune induced nephrotic syndrome brought on by Hg exposure (see below) in sensitive individuals, effects on the kidney appear minor or are unobserved at relatively low levels of occupational exposure.

Renal damage has been monitored above 100 μg Hg/L urine by observing proteinurea (Stewart et al. 1977) and excess excretion of N-acetyl glucosaminidase (Foa et al. 1976). Above 50 μg Hg/L the large size enzyme β-galactosidase (Foa et al. 1976; Schuckmann 1979; Stonard et al. 1983; Naleway et al. 1991) correlated with exposure. Based on these and other studies, a no-observed-effect-level for nephrotoxicity of 50 μg/g creatinine in urine has been proposed (Roels *et al.* 1985). Most of the control subjects in these and other occupational studies of Hg-induced renal dysfunction had urine Hg concentrations in the same range, or higher, than non-occupationally exposed persons with amalgam fillings (Bernard et al. 1987; Barregard et al. 1988; Ehrenberg et al. 1991; Langworth et al. 1992a; Cardenas et al. 1993).

Anneroth *et al.* (1992) reported a decrease in ability to concentrate urine and elevated urine albumin levels among 10 individuals with amalgam fillings. Removal of one 3-surface amalgam filling from each patient significantly decreased average urinary albumin levels. However, substantial amalgam apparently remained, as the mean number of amalgam-filled tooth surfaces reported for the 10 individuals was 31 ± 8. Hence, the results can not be attributed to elimination of amalgam-related Hg exposure. Also, Hg exposure increases for a short time (at least one week) after amalgam extraction (Snapp *et al.* 1989). Therefore, changes observed after only 72 hours, as reported by Anneroth *et al.* (1992), may have resulted from this increase in Hg exposure, as much as from the removal of the filling.

In dentists with an average urine Hg level of 5.8 μg/L to 7.6 μg/L (1985 and 1986 values, respectively), Naleway *et al.* (1991) found no trend in levels of serum β_2-microglobulin (n=58), or urine β-microglobulin (n=20) with increasing urine Hg levels. Also, neither serum creatinine nor urine creatinine clearance (sample sizes not reported) were correlated with urine Hg.

Urine porphyrin levels are indicative of renal Hg content. Porphyrins are formed during the biosynthesis of heme, suggesting that Hg exposure impacts on heme biosynthesis in renal tissue and/or on renal excretion of these substances (Woods *et al.* 1993). The significance of this observation, as evidence of renal toxicity however, is not known. Woods *et al.* (1993) found a dose- and duration-dependent change in the urine porphyrin profile in a group of 56 male dentists selected because their urine Hg level exceeded 20 μg/L (mean urine Hg concentration = 38.4 μg/L). In a study of 15 dentists and dental personnel, Gonzalez-Ramirez et al. (1995) found that porphyrin profile prior to administering the chelating agent 2,3-dimercaptopropane-1-sulfonic acid (DMPS) correlated with urine Hg level after the chelating agent was administered.

It was concluded that generalized renal dysfunction, aside from possible auto-immune induced nephrotic syndrome (see below), is not anticipated to occur at levels of Hg exposure associated with dental amalgam.

7.4 Immunotoxicity

Although the overall incidence of allergy to amalgam is considered by some authors to be low in the population as a whole, data suggest that the incidence of contact hypersensitivity may exceed 15% for that portion of the population with amalgam fillings, and this incidence may increase with both the number and age of fillings. In a general survey of dermal contact hypersensitivity to ammoniated Hg (Rudner *et al.* 1973), 5% of those tested displayed a positive reaction. In that study, possible differential sensitivity between those with and those without amalgam fillings was not examined. White and Brandt (1976) reported an increasing incidence of contact hypersensitivity to mercuric chloride from freshmen through senior class dental students, suggesting increased sensitivity with increasing duration and/or intensity of Hg vapour exposure. Miller *et al.* (1987) reported a similar trend for second year through fourth year dental students, although first year students had a rate of sensitivity exceeding that of second year students. Miller *et al.* (1987) observed a significant positive association between dermal hypersensitivity to mercuric chloride and the number of amalgam fillings in subjects, with the incidence of reaction ranging from 25.6% for those with 0 to 4 fillings, to 44.3% for those with 10 or more fillings,

and an overall incidence of 31.6%. Djerassi and Berova (1969) observed a significant association between dermal sensitivity to Hg and the average age of subjects' amalgam fillings. The incidence of positive reaction was 0% in controls (persons with no amalgam fillings), 5.8% in those with fillings less than 5 years old, and 22.5% for those with amalgam fillings greater than 5 years. Overall, 16.1% of those with amalgam fillings had a positive reaction.

Other evidence confirms that some individuals are directly allergic to Hg compounds upon dermal patch test (Osawa *et al.* 1994; Handley *et al.* 1993). Some persons are allergic to dental amalgam specifically (Finne *et al.* 1982; Duxbury *et al.* 1982). Occupational allergic contact dermatitis from metallic Hg has also been reported (Kanerva *et al.* 1993).

Occupational studies of immunologic reaction from exposure to Hg vapour report variable results. Depending on the intensity and duration of exposure, and on the parameters measured, results have suggested no response (Bernard *et al.* 1987; Langworth *et al.* 1992; Cardenas *et al.* 1993), immune inhibition/suppression (Bencko *et al.* 1990; Langworth *et al.* 1993), or stimulation/activation (Bencko *et al.* 1990; Cardenas *et al.* 1993; Queiroz *et al.* 1994). Immune response to Hg exposure apparently disappears after cessation of exposure (Ellingsen *et al.* 1994). In a study of 41 Swedish adolescents aged 15 years (21 males, 20 females), Herrstrom *et al.* (1994) found no association between most parameters (22 of 23) of cellular and humoral immunity and either amalgam load or plasma Hg concentration. Only immunoglobin IgA was slightly higher in individuals with higher plasma Hg levels (>0.36 μg/L), and this was not statistically associated with amalgam load.

As with occupational studies following inhalation, animal studies of Hg ingestion indicate variable effects on the immune system. These effects are influenced by the type of Hg, and by the species and/or strain of animal tested. Again, depending on the parameter measured, indicators of immune suppression (NTP 1993, Dieter *et al.* 1983), activation (Hultman and Johansson 1991, Hultman and Enestrom 1992) or no apparent effect (Hultman and Johansson 1991) have been reported.

In a review of immunotoxicity studies involving inorganic forms of Hg, the WHO (1991) concluded that the most sensitive adverse immunotoxic effect of mercuric Hg was the formation of Hg(II)-induced auto-immune glomerular nephritis, the first step being the production and deposition of IgG antibodies to the glomerular basement membrane. This effect has been observed in a few individuals occupationally exposed to Hg vapour (Tubbs *et al.* 1982), 3 persons with amalgam fillings (Anneroth *et al.* 1992), as well as in persons using a Hg-containing skin lightening cream (Lindqvist *et al.* 1974; Kibukamusoke *et al.* 1974).

Studies in animals indicate this effect may be species/strain specific, or that a genetic predisposition may be necessary for this auto-immune effect. The brown Norway rat appears susceptible to this effect compared to other species and strains (animal studies reviewed by ATSDR 1994). This effect has also been observed in inbred female SJL/N mice (Hultman and Enestrom, 1992). In another study with genetically Hg-susceptible, inbred female SJL/N mice, implantation of dental amalgam into the peritoneal cavity induced systemic auto-immunity (Hultman *et al.* 1995). Components of the amalgam other than Hg could not be excluded from a potential causal role in the observed reactions.

At this time, it is not possible to estimate the proportion of the population with potential genetic predisposition to auto-immune induced glomerular nephritis due to Hg exposure. However, it is anticipated to be small, given the apparent low incidence of reporting of the effect in occupationally exposed individuals, and those using skin lightening creams containing Hg. There are insufficient quantitative human data on the incidence of, or susceptibility to, auto-immune induced glomerular nephritis to establish a reference dose for Hg vapour emitted from dental amalgam on the basis of this effect.

7.5 Neurotoxicity

Both peripheral and central nervous system effects are associated with Hg vapour exposure. Overt clinical signs of nervous system impairment, including tremor and the various symptoms associated with chronic mercurialism, generally occur at air levels exceeding 100 μg/m^3 (reviewed by WHO 1991) or in association with urine Hg concentrations of 100 μg/L or more (discussed by Echeverria *et al.* 1995). Below these levels which are known to cause clinical symptoms, 'pre-' or 'sub-' clinical impairment of peripheral nerve conduction, intention tremor of the extremities, and impacts on cognitive functions and mood state, have been reported. Negative results (i.e. no effects) have also been reported in this lower exposure range.

Singer et al (1987) reported reduced median nerve conduction velocity in a group of 16 chloroalkali workers relative to controls. A dose-dependent decrease in conduction velocity was observed with blood Hg concentration ($p<0.002$) and, to a weaker degree, with urine Hg concentration ($p<0.06$). Mean urine Hg concentration in exposed workers was 508 μg/L. Likewise, Levine *et al.* (1982) reported a dose-dependent increase in ulnar nerve distal latency (i.e. reduced nerve conduction velocity) in 18 male chloralkali workers with an average spot urine Hg level of 290 μg/L. Shaprio *et al.* (1982) also reported reduced peripheral nerve conduction velocities in a group of 23 dentists with detectable (as measured by X-ray fluorescence) tissue (neck and wrist) loads of Hg, compared to dentists with no detectable tissue Hg levels. The levels of exposure in this study can not be directly compared or converted to urine or room air Hg levels for comparison to other studies.

Fawer *et al.* (1983) reported increased intention tremor of the forearm in a group of 26 male industrial workers compared to age-matched controls. Time-weighted average urine Hg concentration in the exposed group was 20 ± 2 μg Hg/g creatinine compared to 6.0 ± 1.2 μg Hg/g creatinine in controls. Air Hg concentration at the time of testing was 26 ± 4 μg Hg/m^3. Verberk *et al.* (1986) reported increased tremor of the finger in 25 subjects with relatively low occupational Hg exposure (mean urine Hg concentration = 35 ± 19 μg Hg/g creatinine). Roels *et al.* (1982) reported increased tremor and reduced hand-eye coordination in a group of 43 Hg-exposed male workers (mean urine Hg concentration = 95.5 μg Hg/g creatinine) relative to 47 controls (mean urine Hg concentration = 1.3 μg Hg/g creatinine), although no dose-response relationship was evident in the exposed workers. Some reduced hand/arm steadiness was observed for urine Hg levels less than 50 μg/g creatinine.

No significant difference in arm tremor, hand-eye coordination, or reaction time was reported by Schuckmann (1979) in a study of 39 male chloralkali workers with an average urine Hg level of 108 μg/L relative to matched controls (urine, blood and air Hg levels not reported for control subjects). Similarly, Langworth *et al.* (1992b) reported no significant difference in forearm tremor in a group of 89 male

chloralkali workers with a median urine Hg concentration + 25 µg/L (range: 0.5-83), compared to 75 controls with a median Hg concentration + 2 µg/L (range: <detection limit - 8).

Impairment of, or impact on, the central nervous system has also been reported at levels of exposure below 100 µg Hg/L urine and/or 100 µg/m^3 (reviewed by Echeverria *et al.* 1995, WHO 1991). Significant differences between exposed and control groups have been reported in most occupational studies of cognitive function, indicating that no clear 'no- observed-effect-level' can be identified from neurobehavioral studies of occupational Hg vapour exposure, as can be for nephrotoxicity.

Piikivi and Tolonen (1989) reported slower and attenuated electroencephalograms (EEGs), particularly of the occipital region, in 41 chloralkali workers exposed to Hg vapour for an average of 15.6 years. The average time-weighted whole blood Hg concentration in exposed workers, derived from routine occupational health surveys conducted a the plant, was 58.0 ± 26.5 nmol Hg/L blood (11.6 ± 5.3 µg Hg/L blood). Urine Hg concentration at the time of testing averaged 19.4 ± 12.4 µg Hg/L in the exposed group, and 1.8 ± 1.3 µg Hg/L in controls. Based on the long-term blood monitoring data, Piikivi and Tolonen (1989) estimated that workplace air concentrations had averaged about 25 µg/m^3 .

Echeverria et al. (1995) evaluated neurobehavioral performance in 19 dentists with urine Hg concentrations in excess of 20 µg Hg/L (mean = 36.4 ± 20.0 µg Hg/L), relative to 20 dentists with Hg urine levels <0.5 µg Hg/L. Overall poorer performance among Hg-exposed dentists in cognitive and motor function tests was reported, based on pooled or composite test scores. Ngim et al (1992) studied neurobehavioral performance using a battery of tests in 98 Singapore dentists (60 males, 38 females) compared to 54 controls. These data were further analyzed by Foo *et al.* (1993). Mean Hg concentration in the dental offices at the time of the study was 14 µg/m^3 (range 0.7 to 42 µg/m^3). Composite test scores (Z scores) reflected a positive exposure-response association (i.e. as occupational Hg exposure increased, degree of impairment increased). A positive association between exposure duration and impairment was also reported.

Gonzalez-Ramirez *et al.* (1995) reported deficits in tests of attention and perception in a group of 10 dental technicians with an average urine Hg level of 29.7 ± 6.7 µg/L. Echeverria *et al.* (1995), Ngim *et al.* (1992) and Gonzalez-Ramirez *et al.* (1995) reported statistically-significant, dose-dependent increases in impairment of some or all of the neurobehavioral tests. Gonzalez-Ramirez *et al.* (1995) reported improved performance among Hg- exposed subjects in a test of coordination (one hole pin test). However, occupational requirements and/or practice of fine motor skill in the exposed group relative to the controls (nondental personnel) may explain this observation.

In other studies involving dentists and dental workers, Shapiro *et al.* (1982) and Uzzell and Oler (1986) reported impairment in visuographic recognition but no apparent impact on general intelligence, as assessed by the Weschler Adult Intelligence Scale. Ngim *et al.* (1992) also reported no significant difference between dentists and controls in composite Z scores based on 4 tests of intelligence. Methods used by Shapiro *et al.* (1982) and Uzzell and Oler (1986) for measurement of Hg exposure (X-ray fluorescence) prevent comparison of exposure levels to those of Echeverria *et al.* (1995), Ngim *et al.* (1992), Gonzalez-Ramirez *et al.* (1995) and others.

Roels *et al.* (1985) found no significant differences between Hg-exposed industrial workers (131 males; 54 females) and matched control subjects in short term memory, critical flicker fusion, simple

reaction time and colour discrimination. Urine Hg levels ranged from 7 to 272 μg/g creatinine for males and 7 to 89 μg/g creatinine in females.

Mood changes, depression and anxiety are common in chronic mercurialism (Uzzell and Oler 1986) and are also consistently reported in studies of occupational exposure in the range of 30 to 100 μg Hg/L urine (Gonzalez-Ramirez *et al*. 1995), levels of Hg exposure not sufficient to cause clinical mercurialism. A variety of recent studies have investigated psychological factors such as mood, anxiousness/distress, aggression and various self-reported symptoms as a function of Hg exposure. A variety of these reports relate to dentists or dental care workers.

Shapiro *et al*. (1982) and Uzzell and Oler (1986) reported heightened distress in studies of dentists (Shapiro *et al*. 1982) and dental auxiliary workers (Uzzell and Oleo 1986). Ngim *et al*. (1992), in a study of dentists (n=98; mean Hg exposure = 14 $\mu g/m^3$; range 0.7 to 42 $\mu g/m^3$) from Singapore, found dentists to have a more aggressive mood than controls, and a dose/duration dependent increase in aggressive mood with increasing Hg exposure was observed. Gonzalez-Ramirez *et al*. (1995) found dose-dependent associations between urine Hg levels (n=10; mean = 29.7 ±6.7 μg Hg/L) and anger and confusion, as well as with self reported symptoms of headache, emotional problems and comprehension. Similarly, Echeverria *et al*. (1995) observed, in dentists, dose-dependent associations of urine Hg levels (n=19; mean = 36.4 ± 20.0 μg Hg/L) with tension, fatigue, confusion, lack of vigour, and depression, as well as with symptoms related to emotion and concentration. In this latter study, a dose-dependent impact on vocabulary (verbal skill) was also reported.

Apparent alteration of mood has also been reported for industrial workers with relatively low Hg exposure. Liang et al. (1993) found fatigue and confusion to be greater in 88 industrially exposed workers (mean urine Hg = 24 ± 6 μg/L) compared to 70 matched controls (mean urine Hg = <detection limit). Based on self-reported symptoms, Roels *et al*. (1985) reported memory disturbances (males and females), fatigue (males), depressive feelings (females), disturbed sleep (males), and increased irritability (males) among 131 male and 54 female industrial workers with Hg exposure, compared to matched controls. Mean urine Hg levels were: males exposed - 51.5 ± 43.5 μg/g creatinine; male controls (n=114) - 0.9 ± 0.9 μg/g creatinine; females exposed - 36.5 ± 15.7 μg/g creatinine; female controls (n=48) - 1.7 ± 1.5 μg/g creatinine. Langworth *et al*. (1992b) reported increased tiredness, confusion and neuroticism among 89 Hg-exposed chloralkali workers compared to 75 controls. Only neuroticism demonstrated a significant dose-response association with blood Hg levels. Median urine Hg concentration for exposed workers in this study was 25.4 (range: + 0.5 - 83) μg Hg/g creatinine. Median urine Hg in controls was 1.9 (range: <detection - 7.6) μg/g creatinine. Piikivi and Hanninen (1989) reported higher incidence of memory disturbance, sleep disorders, anger, fatigue and confusion for chloralkali workers (n=60) with an average urine Hg + 17 ± 11 μg/L compared to matched controls (mean urine Hg + 2 ± 1.5 μg/L), although rotating shift work appeared partly, but not totally, responsible for these differences.

Despite the less objective nature of these parameters, these numerous studies demonstrate consistency in Hg exposed individuals. Virtually all the studies examining these effects report significant differences between exposed and control subjects, often with significant dose-response associations, indicating that a no-observed-effect-level can not, as yet, be demonstrated.

7.6 Mercury and neurological/neuromuscular disease

Hg is a known CNS toxicant (WHO 1990, 1991), and levels of Hg in autopsied brain tissues are positively correlated to the number of amalgam tooth surfaces (Nylander *et al.* 1987; Eggleston and Nylander 1987; Weiner and Nylander 1993; Friberg *et al.* 1986). Therefore, hypotheses have been postulated linking amalgam and Hg exposure to various neurological or neuromuscular diseases including Alzheimer's Disease (AD) (Duhr *et al.* 1991; Lorscheider *et al.* 1994b, 1995), Amyotrophic Lateral Sclerosis (ALS) (Khare *et al.* 1990; Kasarskis *et al.* 1987; Adams *et al.* 1983), multiple sclerosis (MS) (Clausen 1993; Siblerud and Kienholz 1994) and Parkinson's Disease (PD) (Ngim and Devathason 1989).

The area of greatest study, and therefore with the largest data base for evaluation, is the hypothesized link between Hg exposure and AD. Therefore, only AD is discussed and examined here.

7.6.1 Alzheimer Disease

AD is a degenerative dementia initially affecting memory function but gradually progressing to confusion and disorientation, increased dependency, personality changes, and loss of verbal communication and physical deterioration in more advanced stages (Berg and Morris, 1994). Confirmation of diagnosis is only possible upon histological examination of brain tissues after death, with observation of sufficient densities of neurofibrillary tangles (NFTs) and/or amyloid plaques (Terry *et al.* 1994).

A variety of chemical elements have been reported to be imbalanced in AD brains (reviewed by Markesbury and Ehmann 1994). Elements that have been postulated to play a possible role in this disease include aluminum, bromine, cadmium, cesium, chlorine, iron, lead, Hg, molybdenum, nitrogen, phosphorus, rubidium, silicon, sodium and zinc. In all cases, however, data are equivocal and the postulated role of each or any of these elements in AD remain hypotheses only (Markesbury and Ehmann, 1994).

Ehmann *et al.* (1986) reported higher Hg concentrations in bulk brain samples from AD patients than in age-matched controls. Thompson *et al.* (1988) reported higher levels of Hg in the nucleus basalis of Meynert (nbM) from AD brains than age-matched controls. Wenstrup et al (1990) reported higher levels of Hg in the microsomal fraction of brain samples from AD brains compared to age-matched controls. These studies are the primary basis for the hypothesized role of Hg in the etiology of AD. However, these studies have methodological and statistical problems that preclude any conclusions regarding the validity of this hypothesis.

In the study of Ehmann *et al.* (1986), three serious methodological discrepancies preclude the conclusion of any causal or statistical association between Hg levels and AD. Sample size was small. For comparison of bulk brain samples, samples were collected from 14 AD brains, versus 28 age-matched control brains. For comparison of grey and white matter Hg levels, samples from only 4 AD brains and 3 control brains were studied. For statistical analysis of differences between AD and control brains, total number of samples analysed was used rather than number of patients or controls. In this study, several samples were collected from each brain. For comparison of bulk brain samples, an apparent average of 3.8 samples from each control brain and 4.8 samples from each AD brain were analysed. For comparison of grey and white matter, an apparent average of 4.7 samples from each control brain and

6.8 samples from each AD brain were analysed. The small sample sizes used, the apparent unequal number of samples collected from each individual brain (control or AD), and the greater average number of samples collected from AD versus control brains raise significant questions regarding the validity and interpretation of any differences, statistically significant or otherwise, in this study. The Hg data, and the subsequent statistical analysis, were inappropriately weighted, and statistical influence by outliers is likely.

It should also be noted that the differences in Hg concentration between control and AD brain tissues in the study of Ehmann *et al.* (1986) were not controlled for potential concentration through loss of tissue mass. The brain of an AD patient is known to shrink, losing both protein and total mass (Terry *et al.* 1994). This would result in an apparent increase in concentration of the Hg contained in the brain due to diminished tissue mass, not increased Hg uptake. Therefore, conclusions drawn in this paper that AD brains have higher Hg than age-matched controls is questionable, based on the data reported.

Thompson et al (1988) reported a statistically significant higher Hg concentration in the nucleus basalis of Meynert (nbM) from AD brains than from age-matched control brains. As with the study of Ehmann et al (1986), sample size was small (n=11 AD brains, n=11 control brains), and the potential for chance variation was high. Also, as mentioned previously, there was no correction for possible increased concentration in the AD brain due to tissue loss. The authors did normalize element (including Hg) concentrations to the nitrogen (N) levels in the various tissues, as a measure of tissue protein content. The authors reported generally that some of the observed AD-control differences dropped from significance, especially in the small nbM data set, when the N-normalized data were statistically processed. However, those N-normalized data were not presented.

Normalization for N content assumes that loss of N is an adequate and direct measure of total tissue loss. However, loss of lipids and water (particularly when reporting tissue concentrations on a fresh weight basis), among other tissue components, will not be reflected in measurements of N. These tissues do, however, factor into the measurement of the concentration of Hg on a ng Hg per g total tissue fresh weight basis. Therefore, no conclusions can be drawn as to the statistical or biological significance of the reported differences in Hg content of AD and control brain tissues.

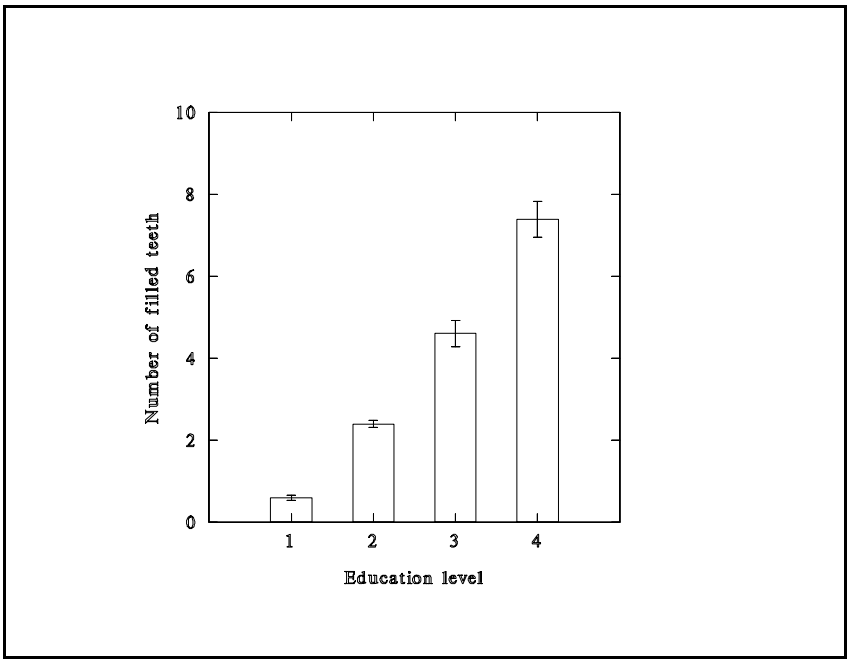
Wenstrup et al (1990) reported that the Hg level in the microsomal fraction of AD brains was statistically significantly higher than in control brains. As with previous studies discussed above, sample size was small (n=10 AD brains, n=12 control brains) and the possibility of chance variation was high. Again, therefore, no conclusions can be drawn as to the statistical or biological significance of the reported differences in Hg content of the microsomal fractions of AD and control brain tissues.

It is unclear whether or not the studies cited above are wholly independent of one another. All three studies were conducted at the same institution, by the same base group of researchers. This, combined with the similarity of sample size in all three studies, suggests that these are dependant data sets, collected from the same patient and control brain tissue bank. Therefore, the potential dependency of these data further reduce the weight of evidence supporting a hypothesized role of Hg in the etiology of AD.

Other evidence also reduces the weight of evidence in support of an etiological role for Hg exposure in AD. Vance *et al.* (1988) reported a significantly lower concentration of Hg in the nails of AD patients compared to controls. This study provided stronger evidence in support of a general element imbalance in AD patients rather than increased exposure to any particular element. There is significant data and information associating rubidium, zinc, bromine and aluminum to AD, not only Hg (Markesbury and Ehmann 1994). Markesbury and Ehmann (1994) also indicate that evidence points to element imbalances, rather than excess exposure *per se*, as hypotheses to be explored.

Level of education is an apparent risk factor in the etiology of AD (Katzman and Kawas, 1994), with lower education linked to an increased risk of the disease. However, data from the Nutrition Canada Survey (Health Canada, unpublished) indicate that the number of filled teeth increases (Figure 7.1) with higher education, likely due to better dental care and reduced loss of teeth. The higher incidence of filled teeth with higher education level should contribute to an increase in risk of AD, not a decrease, if Hg exposure from dental amalgam (i.e. more amalgam-filled teeth) contributes significantly to AD risk.

Figure 7.1. Number of filled teeth as a function of education level for persons 40 years of age and older (as of 1970-72). 1= 0 to 6 years of grade school; 2 = 7 to 13 years of grade school; 3 = some post-secondary education; 4 = college and university education.



In a recent study from Sweden (Fratiglione *et al.* 1993), increased alcohol consumption was strongly associated with increased risk of AD (odds ratio=4.4; CI = 1.4-13.8). However, increased alcohol consumption has been associated with reduced retention of Hg (Nielsen-Kudsk 1965; Hursh *et al.* 1980; Khayat and Dencker, 1984) and reduced concentrations of Hg in the brain (Weiner and Nylander 1993; Nylander *et al.* 1987) . Therefore, alcohol consumption would be expected to reduce the risk of AD if Hg levels in the brain were a significant etiological factor.

β-tubulin is important in the proper growth and formation of neurons (Falconer *et al.* 1994). Methyl Hg is known to inhibit β-tubulin (Brown *et al.* 1988). Therefore, methyl Hg exposure should also be an etiological factor in AD, along with elemental Hg, if inhibition of this enzyme is the mechanism of action for Hg's purported role in AD (see below). Fish consumption is the primary source of exposure to methyl Hg (WHO 1990). Therefore, countries with a high per capita fish consumption rate would also be expected to have either a higher per capita incidence of AD, an earlier average age of onset of clinical diagnosis of the disease in the population as a whole, or a greater rate of increase in incidence of the disease with increasing age.

Available epidemiological data provide no unequivocal evidence of a link between AD rates and potential methyl Hg exposure via fish consumption. It has been observed that the relative age-specific incidence per capita, and the rates of increase in incidence with age are very similar for several studies and among different countries (Katzman and Kawas, 1994), including Japan, the latter country known to have a high rate of fish consumption per capita (per capita commercial fish supply 72 kg/year (FAO 1994)). Japan's apparent rate of fish consumption (based on fish supply statistics) is greater than Canada, the U.S. and all European countries for which data were reported (see FAO 1994). In a review and comparison of AD studies from 10 countries by Katzman and Kawas (1994), one epidemiological study of AD in Japan (Ueda *et al.* 1992) did report one of the highest age-specific incidence rates and one of the greatest rates of increase in incidence of AD with age. However, a second Japanese study (Fukunishi *et al.* 1991) reported the lowest age-specific incidence rate and lowest rate of increase in incidence of AD with age among these same 10 studies (see Katzman and Kawas, 1994). No data were located to compare the average age of clinically diagnosable signs of AD on a country by country basis.

7.6.2 Hypothesized mechanism of action for Hg in the etiology of AD

A mechanism of action, at the biochemical level, has been postulated from *in vitro* and *in vivo* evidence which is consistent with the hypothesis that Hg exposure is an etiological factor in AD. Elemental Hg is oxidized to Hg^{2+} in brain tissue following penetration of the blood-brain barrier (WHO 1991). *In vitro*, Hg^{2+} alters ATP rybosilation of β-tubulin (Palkiewicz *et al.* 1994) and also inhibits the GTP phosphorylation of β-tubulin (Duhr *et al.* 1991). Both reactions indicate potential interference with cellular and biochemical homeostasis in neurons. *In vivo*, reduction in ATP rybosilation has been observed in the brains of rats intraperitoneally injected with $HgCl_2$ (Palkiewicz *et al.* 1994). Also, reduced affinity of rat brain β-tubulin for GTP (Lorscheider *et al.* 1994) has been observed following exposure of live animals to Hg vapour. Reduced affinity for GTP is also observed in β-tubulin extracted from AD brain samples (Khatoon *et al.* 1989).

These data provide indirect support for Hg's hypothesized role in AD. Research continues to elucidate this mechanism, toward demonstrating histological changes in the brains of laboratory animals consistent with that of AD. However, no Hg-induced, dose-dependent incidence of neurofibrillary tangles

(NFTs) nor amyloid plaques in any animal model has been reported. Also, neuronal proteins other than tubulin, such as the microtubule-associated protein Tau (Bancher *et al.* 1989), have been hypothesized as proteins involved in NFTs. In fact, Tau is more structurally similar to NFT than to tubulin (Ruben *et al.* 1993). Other authors hypothesize that formation of amyloid plaques is the primary cause of AD (Joachim and Selkoe, 1992), not necessarily NFTs.

It is apparent that many questions need resolution before the hypothesis that Hg exposure induces AD can be proved or disproved. Although the data demonstrating higher Hg levels in brain tissues of AD patients are weak, one step (at the biochemical level) in the postulated mechanism of action has been demonstrated both *in vitro* and *in vivo*. As mentioned previously, the etiology of AD is yet to be elucidated and a variety of biochemical modes of action are being investigated. The uncertainty surrounding this hypothesis is large, and is such that the postulated link can not be confirmed or refuted.

8.0 Tolerable Daily Intake

To date, no tolerable daily intake (TDI) has been established in Canada for non-occupational exposure to Hg vapour via inhalation. A TDI is defined as that dose to which it is believed an individual can be exposed daily over a lifetime without deleterious effect (HC, 1994). A TDI is not, however, necessarily applicable to hypersensitive individuals for which extraordinary control measures are required (HC, 1994). A TDI is established by applying uncertainty factors to a no-observed-adverse-effect-level (NOAEL) or lowest-observed-adverse-effect-level (LOAEL) for a critical endpoint identified from an investigation of the most appropriate target organism (in this case, humans).

Various international agencies (reviewed by IARC 1993) have proposed or established occupational exposure limits for Hg in work room air, ranging from 5 to 150 $\mu g/m^3$. However, effects on neurobehavioral and psychomotor performance, objectively detectable tremor and nerve conduction velocity, and a variety of consistently reported symptoms are observed in the 20 to 50 $\mu g/m^3$ exposure range (corresponding to + 20 to 50 µg Hg/L or µg/g creatinine). This, combined with the fact that available data do not indicate a clear no-observed- effect-level, suggests that effects will occur in some proportion of the occupationally-exposed population at these occupational exposure limits. Therefore, these limits do not provide an appropriate basis for establishing a non-occupational exposure limit for Hg vapour. This is particularly true with respect to exposure from amalgam, as this latter source is continuous compared to the intermittent exposure common to occupational environments (8 hours per day, 5 days per week, 48 weeks per year, for example).

In a review of occupational studies, ATSDR (1994) identified the study of Fawer et al. (1983) as the most methodologically-sound study for derivation of a minimum risk level (MRL) for chronic inhalation of Hg vapour. Fawer et al. (1983) reported a significant increase in hand tremor in 26 male employees exposed to Hg vapour for an average of 15.3 years (range: 1 to 41 years), compared to 25 controls. The average Hg concentration in the air for exposed workers at the time of testing was 26 ± 4 $\mu g\ Hg/m^3$ (variation over duration of exposure not reported). Concentrations of Hg in the air for control subjects were not reported, but average blood and urine Hg levels in controls were 2.5 and 3.3 times lower, respectively, than average levels in the exposed workers.

This same study can be used to derive a proposed TDI for Hg vapour. Assuming continuous exposure at the reported level of 26 μg Hg/m^3, an 8 hour inhalation volume of 6.6 m^3 (U.S. EPA 1989), 80% absorption of inhaled Hg (WHO 1991), and adjusting for a 5 day work week, an equivalent daily dose can be calculated as:

Equivalent absorbed dose = 26 μg Hg/m^3 X 6.6 m^3 X 0.8 X 5 days/7 days = 98.1 μg Hg/day

Applying safety factors (after ATSDR 1994) of 10 for use of a lowest-observed-adverse-effect-level rather than a no-observed-adverse-effect-level (Fawer et al. (1983) did not detect a threshold for affects in the exposed group), and 10 for inter-individual variation/sensitivity, provides a proposed TDI of:

proposed TDI = 98.1 μg Hg/day / (10X10) = 0.98 μg Hg/day for a 70 kg adult,
or 0.014 μg Hg/kg body weight/day

8.1 Tolerable urine concentration

The study of Echeverria et al. (1995) can be employed to derive a concentration of Hg in urine which represents an exposure likely to be free of neuropsychological effects. Extensive data exist on urine Hg concentrations associated with the presence of dental amalgam fillings to which a tolerable urine Hg concentration could be directly compared.

Echeverria et al. (1995) evaluated neurobehavioral performance in 19 dentists with urine Hg concentrations in excess of 20 μg Hg/L (mean = 36.4 ± 20.0 μg Hg/L), relative to 20 dentists with Hg urine levels <0.5 μg Hg/L. The mean concentration of 36.4 μg Hg/L urine represents a lowest-observe-adverse-effect concentration. Overall poorer performance among Hg-exposed dentists in cognitive and motor function tests was reported, based on pooled or composite test scores. A statistically-significant dose-dependent increase in impairment of verbal skill was also reported. They also observe dose-dependent associations of urine Hg levels with tension, fatigue, confusion, lack of vigour, and depression, as well as with symptoms related to emotion and concentration.

An uncertainty factor of 10 must be applied to account for the reported lowest-observed-adverse-effect concentration rather than a no-observed-adverse-effect concentration. Echeverria et al. (1995) did not detect a threshold for effects in the exposed group. To account for inter-individual variation/sensitivity, the study of Echeverria et al. (1995) provides for a direct estimate of inter-individual variation in response. For all objectively measured variables (cognitive function, neuromotor coordination, mood), an approximate estimate of inter-individual variation was determined as:

$$IV_i = \frac{\text{parameter}_i \text{ mean value} + (3 \text{ X standard deviation})}{\text{parameter}_i \text{ mean value}}$$

where IV_i is the estimated inter-individual variation ratio for $parameter_i$, $parameter_i$ demonstrating a significant association with Hg exposure. From Echeverria *et al.* (1995) the mean IV_i value was 2.4 (for 12 parameters) with a maximum value of 4.7. Based on this information, an uncertainty factor of 5 (maximum value of IV_i rounded to nearest whole number) was deduced. Therefore, the tolerable urine concentration (TC) based on the study of Echeverria et al. (1995) would be:

TC = (36.4 μg/L)/50 = 0.73 μg Hg/L ± 0.7 μg/L

9.0 Discussion and Risk Characterization

The two methods of exposure estimation employed here agree well, given the different theoretical approaches and different variables employed. Method 1 (after Olsson and Bergman 1992) estimated that Canadian adults with amalgam filled teeth receive an average daily absorbed dose of 3.74 μg. Method 2 (after Richardson *et al.*, 1995) estimated that adults with filled teeth would receive a daily absorbed dose of 3.38 μg from amalgam alone. Estimates of average daily dose by age group were consistently higher by method 1 compared to method 2. The estimated average adult daily absorbed dose of all forms of Hg from all sources was 9.4 μg.

This is remarkably good agreement between the two methods, which were developed independently by different evaluators, and given the completely different theoretical bases for the methods used. These estimated exposures also agree very well with the data of Skare and Engqvist (1994) who determined that an average daily exposure of 12 μg occurred among nine adults with an average of 47 amalgam surfaces. Assuming 2 surfaces per filled tooth (Nylander *et al.* 1987), then these nine individuals had an average of approximately 23 or 24 filled teeth. Therefore, data of Skare and Engqvist (1994) suggest a dose of about 4 μg for an average of 8.65 filled teeth, the average number of filled teeth in the Canadian adult population (see Table 4.1). As a result, the methods employed herein were considered to have acceptable accuracy for derivation of distributions of exposure across the population.

Based on the model derived from Olsson and Bergman (1992), it is possible that ingestion of amalgam particles and Hg species in saliva may contribute an average of 40% of exposure to Hg from amalgam (Table 5.4). The pharmacokinetics of Hg are different for inorganic Hg which is ingested, compared to inhaled Hg vapour. In particular, relatively little of the ingested Hg would cross the blood-brain barrier and reach the CNS, the site for critical effects. Therefore, the contribution of ingestion to amalgam-related Hg exposure should be resolved.

It is apparent from the exposure assessment based on Richardson et al. (1995) that amalgam contributes significantly to daily Hg exposure, in the range of 30 to 50% (Table 5.14). This makes amalgam the most significant single source of Hg, compared to food, indoor and outdoor air, drinking water and soil.

The proposed tolerable daily intake of 0.014 μg Hg^0/kg bw/day provides a tentative benchmark against which to compare the dose received from dental amalgam. For all age groups, estimated average daily exposure from amalgam exceeded this dose (see sections 5.2.16 and 5.3.16). These estimates exclude other sources of exposure to Hg^0 such as indoor and outdoor air; these latter sources contributed very little to Hg exposure. For fixed numbers of fillings, the number of fillings predicted by each model not to result in exceeding the TDI are presented in Table 5.15. The lower numbers for the younger age groups reflect the influence of reduced average body weight.

Table 5.15. Number of filled teeth predicted not to exceed an average daily dose of 0.014 µg/kg bw/day.

Age group	Model 1 (after Olsson and Bergman, 1992)	Model 2 (after Richardson et al. 1995)
Toddler	0	1
Child	0	1
Teen	2	3
Adult	2	4
Senior	2	4

These estimates of the number of fillings expected not to result in exceeding the TDI are also in general agreement with the proposed tolerable urine concentration (TC) of 0.7 µg Hg/L. When applied to the data of Skerfving (1991) (see Figure 5.15), and assuming that µg Hg/L + µg/g creatinine (Echeverria et al. 1995), then this urine Hg concentration corresponds to about 5 fillings.

The precise exposure from amalgam may not only be a function of amalgam-filled teeth, but may also be a function of the size and location of these fillings. Filled occlusal surfaces may result in greater exposure than filled lingual or buccal surfaces, due primarily to the impact of chewing and abrasion. Also, teeth with small fillings may result in less exposure than teeth with large fillings. Since quantitative Canadian population data on the size and placement of amalgam fillings did not exist, the assessment herein focused simply on the number of filled teeth. However, Skare and Engqvist (1994) found that the same amount of data variation was explained by either number of filled tooth surfaces, number of occlusal surfaces, or total amalgam surface area. As a result, it is unlikely that more accurate or definitive estimates of exposure would have been derived if one of these other measures of amalgam load were employed for risk assessment.

A variety of uncertainties exist in the data and assumptions made throughout both exposure assessments described herein. The degree of confidence in variables based largely on professional judgement is less than that for empirically-defined variables. However, given the available information, the assumptions made were considered appropriate and defensible.

Uncertainty also exists in the definition of a reliable model for estimating exposures. For this reason, two separate and independent exposure assessment models have been presented. Data also suggest that the number of fillings in toddlers, children and teens may have decreased by 30 to 50% since the collection of data on the incidence of filled teeth in these age groups (1970-72). Therefore, estimates of average exposure arising from amalgam may have over-predicted actual current (1995) exposure by this same amount. Available data on adults and seniors, however, suggest an increase in the incidence of filled teeth since 1970-72, of between 30 and 50%. Therefore, exposure to Hg from amalgam in these age groups may be under-estimated. No Canadian cross-sectional population data, collected later than 1972, exist on the incidence of filled teeth. Therefore, the postulated increase or decrease of numbers of fillings in the various age groups could not be verified. These possible variations in the number of filled teeth in the 1995 Canadian population do not affect estimates of exposure for fixed numbers of fillings.

As yet, no clear threshold for effects is evident from published studies of the neuropsychological or neurobehavioral effects of Hg vapour. Uncertainty factors introduced to derive the proposed tolerable daily intake (TDI) and tolerable urine concentration (TC) may be conservative and result in values for these parameters which are lower than the actual threshold for effects. However, given available information and common regulatory practice in Canada and the U.S., the proposed TDI and TC provide benchmarks for exposure, at or below which adverse effects are not anticipated to occur in the vast majority of the population.

10.0 References

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