Derivation of health-based guidance value

In this guide

Derivation of HBGV for MeHg

57. The original provisional tolerable weekly intake (PTWI) for MeHg (3.3 µg/kg bw) was revised at the sixty-first JECFA meeting to protect the developing fetus from neurotoxic effects (FAO/WHO, 2004). This change was based on

findings from two major epidemiology studies from the Faroe Islands and the Seychelles (FAO/WHO, 2004). The assessments were made on the basis of the evaluations of children at 7 years of age in the Faroe Islands (Grandjean et al., 1997) and 5.5 years of age in the Seychelles (Davidson et al., 1998).

58. A no observed adverse effect level (NOAEL) for neurobehavioural effects of 15.3 mg/kg mercury in maternal hair was established from the Seychelles main cohort study (Davidson et al., 1998). JECFA performed a mathematical analysis of the concentration to response relationship to determine a benchmark dose lower confidence limit (BMDL05) of 12.0 mg/kg mercury in maternal hair in the Faroe Islands (Grandjean et al., 1997; Budtz- Jørgensen et al., 1999; 2000; 2001; National Research Council., 2000; Rice et al., 2003). An average of the NOAEL and BMDL05 from the Seychelles and Faroe Island studies was used (14 mg/kg mercury in maternal hair) as an estimate of the concentration of MeHg in maternal hair that reflects exposures that would have no appreciable effect on the offspring in these two study populations.

59. The concentration of MeHg in maternal hair was converted to mercury in maternal blood using an average overall ratio of 250. Based on this factor, the MeHg concentration in maternal blood that would be expected to have no appreciable adverse effects on the offspring was calculated to be 0.056 mg/L (FAO/WHO, 2004).

60. By use of a one-compartment toxicokinetic model (WHO, 1990), refined to better reflect the situation in pregnant women, JECFA calculated the daily ingestion of MeHg (1.5 µg/kg bw/day) corresponding to a maternal blood mercury concentration that would have no appreciable adverse effects on the offspring in the two study populations (FAO/WHO, 2004).

61. A data-derived factor of 2 for variation in hair to blood ratio of mercury was applied by JECFA. Interindividual variation in toxicokinetics when converting the concentration of mercury in blood to an estimated daily intake was taken into account by a standard factor of 3.2 ($10^{0.5}$). This resulted in an overall uncertainty factor (UF) of 6.4 (FAO/WHO, 2004).

62. Following application of this UF, a PTWI of 1.6 µg/kg bw was established by JECFA (FAO/WHO, 2004).

63. In 2012 the EFSA CONTAM Panel assessed new literature published since the 2004 JECFA evaluation (EFSA, 2012). The CONTAM Panel identified new information on confounding by beneficial factors in fish on associations between

prenatal MeHg exposures and neurodevelopmental endpoints.

64. New developments from the first nutrition cohort of the Seychelles Child Development Study (SCDS) indicated a negative association between prenatal mercury exposure and neurodevelopmental endpoints in children at age 9 and 30 months (Stokes-Riner et al., 2011), but not at 5 years (Strain et al., 2012), whereby it appeared that the positive effects from intake of n-3 LCPUFAs no longer outweighed detrimental effects from MeHg exposure. The studies examined associations between MeHg, maternal nutrition, and children's scores on the Bayley Scales of Infant Development-II test.

65. The CONTAM panel found that, based on results from the newer SCDS nutrition cohort studies, a MeHg concentration of 11 mg/kg in maternal hair was an apparent NOAEL for decreased scores on neurodevelopmental indices after adjustment for prenatal blood maternal n-3 LCPUFAs (Lynch et al., 2011). They considered this a better point of departure than the unadjusted figure of 15.3 mg/kg MeHg in maternal hair previously derived from the SCDS main cohort (EFSA., 2012).

66. For the Faroe Islands cohort, the CONTAM Panel could not identify a more appropriate point of departure than the BMDL05 of 12 mg/kg selected by JECFA (EFSA., 2012).

67. Based on the above, a maternal hair MeHg concentration of 11.5 mg/kg (the mean of the Faroese and Seychelles cohorts) was used as an estimate of the concentration of MeHg in maternal hair reflecting exposures that would have no appreciable effect on the offspring in these two study populations (EFSA., 2012).

68. A factor of 250 was used to convert this to an equivalent concentration of mercury in maternal blood of 46 µg/L (EFSA., 2012).

69. Output from a one-compartment toxicokinetic model determined that a maternal daily dietary mercury intake of 1.2 µg/kg bw corresponded to a maternal blood mercury concentration that was considered to have no appreciable adverse effects on the offspring. By applying a total UF of 6.4 to this value, the CONTAM Panel established a tolerable weekly intake (TWI) for MeHg of 1.3 µg/kg bw expressed as mercury (EFSA, 2012).

Derivation of HBGV for inorganic mercury

70. The first HBGV for inorganic mercury was derived by JECFA in 2011 based on animal studies as human data on the adverse effects to inorganic mercury exposure is limited to case reports or series that do not allow identification of dose-response relationships and hence an HBGV cannot be derived (FAO/WHO, 2011).

71. JECFA agreed that the toxicological database for mercuric chloride was relevant for assessing the health risk of foodborne inorganic mercury.

72. For JECFA's risk assessment the National Toxicology Program (NTP) 1993 rat bioassay study was considered the most informative because it used low-dose exposures to mercuric chloride administered via the oral route. Groups of 10 male and 10 female F344 rats received 0, 0.312, 0.625, 1.25, 2.5, or 5 mg mercuric chloride/kg bw in deionized water (5 mL/kg dose volume) by gavage 5 days/week for 26 weeks. The most sensitive endpoint was found to be relative kidney weight. The BMDLs generated for relative kidney weight were lower than those generated for all other endpoints investigated (FAO/WHO, 2011).

73. The lowest BMDL10 for relative kidney weight increase in male F344 rats was calculated to be 0.11 mg/kg bw per day as mercuric chloride, corresponding to 0.06 mg/kg bw per day as mercury, adjusted from a 5 days/week dosing schedule to an average daily dose and for the percent contribution of inorganic mercury to mercuric chloride dose (FAO/WHO, 2011). After application of a 100-fold UF, JECFA established a PTWI for inorganic mercury of 4 µg/kg bw (rounded to one significant number) (FAO/WHO, 2011).

74. The previous PTWI of 5 µg/kg bw for total mercury, established at the sixteenth JECFA meeting (FAO/WHO., 1972), was withdrawn. The new PTWI for inorganic mercury was considered applicable to dietary exposure to total mercury from foods other than fish and shellfish (FAO/WHO, 2011).

75. In 2012 the EFSA CONTAM Panel evaluated the same evidence as JECFA as well as more recent studies and the Panel agreed with the rationale of JECFA, i.e., setting a HBGV based on relative kidney weight in rats from the NTP 1993 study as the pivotal effect. The CONTAM Panel derived the same TWI for inorganic mercury as JECFA, 4 µg/kg bw (EFSA, 2012).