

Announcement by the Federal Environment Agency

Addendum to “Substance Monograph: Mercury – Reference and Human Biomonitoring Values” of the Human Biomonitoring Commission of the Federal Environment Agency

Opinion of the Human Biomonitoring Commission of the Federal Environment Agency

Introduction

In 1999, the Commission published its monograph on mercury with reference values and human biomonitoring (HBM) values [1]. Acrodynia (morbus Selter-Swift-Feer, Feer’s disease, “pink disease”), which is mercury-associated and may occur in infants and young children, was not taken into account in the derivation of human biomonitoring (HBM) values as it was considered a disease that is very rare today [1]. However, descriptions of cases of acrodynia can still be found in the recent medical literature [2]. This prompted the Commission to once again look into the effects of mercury (Hg) on humans, particularly the link between blood mercury levels and the occurrence of acrodynia in children.

History of acrodynia

The name “acrodynia” is derived from Greek, “pain in the extremities”, a typical symptom. Selter was the first author to describe the disease, presenting eight cases that occurred between 1898 and 1903 [3]. Acrodynia was long thought to be caused by infections [4]. Bilderback published the first detailed description of the disease in 1925 in the USA [5]. From studies from England, Australia and the USA it was concluded that acrodynia most frequently occurs in children up to two years of age, with a maximum at seven months [6]. Between 1939 and 1948, 585 children died of acrodynia in England and Wales, of whom 103 died in 1947 alone [7, 8]. The mortality rate was stated to be approximately 7 %, in a range between 5.5 to 33.3 % [4].

The aetiology remained unknown for half a century until Warkany and Hubbard produced convincing evidence in a large study with 41 patients that acrodynia is caused by mercury [9]. Shortly thereafter, Logan showed in a review of mortality from acrodynia in England and Wales that in 1947 there was a significant mortality increase from 17 to 29 per million; he suspected the cause to be teething powders containing mercury, but could not fully rule out

that the increase was due to a change in diagnostic standards [10]. It remained undisputed, however, that the use of calomel as teething powder (“sweet mercury”) triggered many cases of acrodynia in Anglo-Saxon countries. The fact that only one of around 500 children receiving the same kind of calomel treatment developed acrodynia [11] seems to have delayed recognition of the connection between mercury exposure and acrodynia.

At about the same time, Fanconi and coworkers reported 39 cases of acrodynia in children who had received calomel (mel [GK] honey) as anthelmintic agent, “*Wurmschokolade*” (several individual doses between 150 and 500 mg!), in Switzerland and Germany [7, 12]. The disease manifested itself eight days after treatment. Another review, of 62 acrodynia cases diagnosed between 1926 and 1958 in the Vanderbilt University Clinic, was authored by Chamberlain and Quillian [13]. In the USA, the use of calomel in medicine was banned by the Food and Drug Administration in 1960, not least because of these findings (referred to in [7]). After that time, the frequency of the disease dropped drastically.

In 1980, three small children showing symptoms typical of acrodynia as well as high Hg urinary excretion levels attracted concern in Buenos Aires. The cause proved to be cloth diapers which commercial diaper services had treated with phenyl mercury as fungicide in the last wash cycle. The authors estimated that between 7,000 and 10,000 children were exposed via diapers, with a prevalence of acrodynia of less than 1 per 1,000 children exposed. A striking fact is that cases of acrodynia occurred only after the phenyl mercury dose in diapers had been doubled [14].

Acrodynia today

Acrodynia has many and varied manifestations (see **Overview 1**). Typical manifestations in most cases are: anorexia, weight loss, swelling and discolouration (“pink disease”) of hands and feet, exanthema, pruritus, desquamation on palms and soles, hyperhidrosis, personality change with greater irritability and fretfulness, tachycardia, hypertonia.

Reports of cases of acrodynia can still be found in the recent medical literature [15, 16]. The latest reports from Germany date back only two years [17, 18]. A review up to 2007 was presented by von Mühlendahl [2], who points out the risk of misdiagnosis due to the rareness of the disease. In differential diagnosis, mercury poisoning should be kept in mind in unclear, suspect cases of pheochromocytoma or Kawasaki disease [19, 20].

<p>Overview 1: Manifestations of Acrodynia</p>
<p>Acrodynia is not always accompanied by all of the manifestations listed. The symptoms that are <u>underlined</u> have been reported in most cases.</p>
<p>Psychological, neurological, vegetative manifestations</p>
<p><u>Personality change</u> (irritable, fretful, crying, depressed) <u>Pain</u> (lancinating), swelling of hands and feet Muscular hypotonia, ataxia, paralysis Adynamia, apathy <u>Anorexia</u>, weight loss Somnolence, insomnia, reversal of sleep time Photophobia, irritability <u>Hyperhidrosis at normal temperature</u> <u>Tachycardia, hypertonia</u>, (lab elevated urinary levels of vanillylmandelic acid) Hyperglycemia Tremors</p>
<p>Dermal manifestations</p>
<p><u>Exanthema</u> (morbilliform, rubeoliform, scarlatiniform), <u>pruritus</u> <u>Symmetrical discolouration of the acra</u> (bluish-red, acrocyanosis, "pink-disease") <u>Lamellar desquamation on hands and feet</u></p>
<p>Other manifestations</p>
<p>Hair loss Hypersalivation, gingivitis, dedentition</p>

In **Table 1** we have compiled 47 case reports on 66 acrodynia patients, which were published between 1963 and 2009. It can be seen from the table that today, exposure to mercury vapour in the home – often from unspecified sources of metallic mercury – is reported most often (18 times), followed by exposure to mercury vapour from broken devices (thermometer, barometer, blood pressure gauge, manometer, fluorescent lamps, mirror) (ten times) or to mercury vapour from public-health products (six times). The use of a vacuum cleaner to remove contamination by residues of metallic mercury is out of the question (for example, [22, 22]), since this causes a sharp increase in concentrations of mercury vapour in indoor air.

Although very rare, acrodynia is a disease that still occurs in industrialised countries today [16]. However, a fact to consider in the age of globalisation is that Hg is still being used in toxic quantities in many areas such as in "artisanal" gold mining in large parts of South America, Africa and Asia (with millions of exposed individuals), rituals and religious practices (for example, Santeria and Voodoo) and traditional Chinese and Indian medicine, and that especially children may suffer high exposure from these uses [20]. Only recently, there was a report of a case of acrodynia after administration of a traditional Chinese medicinal product [15]. The cases in Germany reported recently [17, 23] were caused by exposure to metallic mercury.

**Table 1:
 Descriptions of cases of acrodynia following exposure to mercury compounds (in ascending order by Hg concentration in urine)**

No	Hg exposure via	Patient(s) Sex	Patient(s) Age	Time of sampling after exposure	Hg in blood µg/l	Hg in urine µg/l	Reference
1	met. Hg Thermometer, vacuum cleaner	2 m	11 + 14 M	4 M		Not elevated	Chrysochoou et al., 2003 [44]
2	Thermometer	f	32 M			5	Cloarec et al., 1995 [45]
3	Thermometer	f	11 M	2 M		12.6	Velzeboer et al., 1997 [46]
4	met. Hg	m	17 M	1 Tag	10	17	Zurek et al. 2008 [17]
5	met. HG	f	11	2 Tage		21/(24h)	Van der Linde 2009 [16]
6	Thermometer	2 sisters	33 + 20 M	4 M		26,8; 6,9	von Mühlendahl, 1990 [47]
7	Barometer	2 m /1 f	13 + 16 + 11 Y	2-4 M	5.8; 4.4; 13	8,4; 42; 44	Koyun et al., 2004 [48]
8	met. Hg	2 brothers	3 Y+ 20 M	> 1 M	22.4; 11	37.3/(24h)1 9.6/(24h)	Beck et al., 2004 [49]
9	met. Hg	m	8 Y	ca. 4 M		12/(24h) 42.9 µg/g creati-nine	Gattineni et al., 2007 [50]
10	met. Hg	m	10 Y	> 3 M	27.7	34.4/(24h)	Abbaslou et al., 2006 [51]
11	met. Hg (200ml) at home	f	14 M	4.5 M		48 /(24h)	Dinehart et al., 1988 [52]
12	?	f	2 Y	?	< 5	33.2 µg/g create-nine	Michaeli-Yossef et al., 2007 [53]
13	Latex paint (phenyl)Hg	m	4 Y	> 10 D		64.8/(24h)	Agocs et al., 1990 [54]
14	Latex paint (phenyl)Hg	m	4 Y	> 1 M?		65/(24h)	CDC, 1990 [55]
15	Phenyl(Hg)borate oral cavity	2 m	2 J	1.5 M	?, 54	40; 120	Hertl et al., 1982 [56]
16	met. Hg	m	11 M			90/(24h ?)	Swaiman et al., 1971 [57]
17	met. Hg Mirror, vacuum cleaner	m	18 M	ca.3/4 M		70	Curtis et al., 1987 [58]
18	Fluorescent lamp, vacuum cleaner	m	23 M	> 2 M	(43)	73	Tunnessen et al., 1987 [59]
19	met. Hg	m	14 Y	ca. 1 M	22	80	Henningsson et al., 1993 [19]
20	Latex paint (phenyl- Hg)	m	5 Y	> 5 M		90	Hirschman et al., 1963 [60]
21	met. Hg? Vacuum cleaner	m	11 Y	> 3 M	66	123/(24h)	Shih et al., 2001 [61]
22	met. Hg	m	13 Y	2.5 M	20.6	130/(24h)	Karpathios et al., 1991 [62]
23	Chinese medicine	m	11 M	5 M	13.8	150 µg/g create nine	Koh et al., 2009 [15]
24	Manometer	2 brothers	12 + 6 Y	3 M		158/113 µg/g creati- nine	Horowitz et al., 2002 [63]
25	met. Hg	m	3 Y			174 µg/g creati- nine	Borth-Bruhns et al., 2003 [64]
26	met. Hg	m	17 Y		(13)	(210)	de Oliveira et al., 1996 [65]
27	Chinese medicine ?	f	11 Y	?	20	217	Wößmann et al. 1999 [66]
28	met. Hg Manometer, vacuum cleaner	f	30 M	> 2 M		214/(24h)	Foulds et al., 1987 [67]

**Table 1:
 Descriptions of cases of acrodynia following exposure to mercury compounds (in ascending order by Hg concentration in urine)**

No	Hg exposure via	Patient(s) Sex	Patient(s) Age	Time of sampling after exposure	Hg in blood µg/l	Hg in urine µg/l	Reference
29	met. Hg	f	8 Y	2 days	2.9 serum	250	Alexander and Rosario 1971 [68]
30	met. Hg Vacuum cleaner	m	14 Y	>2 M		350/(24h)	Tominack et al., 2002 [69]
31		f	14 Y	3 Mo	34 serum	375	Böckers et al., 1983 [70]
32	Manometer, vacuum cleaner	m / w	4 + 6 Y	?	24; 42	324/(24h); 885/(24h)	Torres et al., 2000 [71]
33	met. Hg (oral and mercury vapour)	f	12	2 days	62; 165 serum	392; 141	Radke 2009 [18]
34	met. Hg ?	4 children	3-6 Y	?	10-20	300-400	Laurans et al., 2001 [72]
35	met. Hg (250 ml)	f	14 J	ca. 2 M	140	520	McNeil et al., 1984 [73]
36	Manometer. Vacuum cleaner	m	9 Y	3 M ?	100	306 µg/g creati nine	Rennie et al., 1999 [74]
37	met. Hg	2 m	10 + 12 Y	5 M		1270; 586	Baughman, 2006 [75]
38	met. Hg	m/f	15 + 13 Y		23; 69	1314; 624 /(24h)	Yeates, Mortesen, 1994 [76]
39	met. Hg	m/f	15 + 11 Y	1 M ?	1500	840; 1500 /(24h)	CDC, 1990 [77]
40	met. Hg (500 ml)	2 f	12 + 16 Y	1-2 M	183; 277	2400/	Sexton et al., 1978 [78]
41	Sidha Medicine	f	2 Y			Toxic range	George et al., 1993 [79]
42	Indian medicine	f twins	22 M	1.5 M	41.8; 35.3		Fayez et al., 2005 [80]
43	met. Hg (5-10 l)	f	10 Y		39		MacLehose et al., 2001 [81]
44	Teething powder from India	f twins	20 M	1 M	35; 42		Weinstein et al., 2003 [20]
45	met. Hg Vacuum cleaner	m	3 J		48		Bonhomme et al., 1996 [82]
46	Diapers Phenyl(Hg) cutaneous	3/509	Median: 14 M				Gotelli et al., 1985 [14]
47	met .Hg	w	3 Y	> 6 M	295		Cherry et al., 2002 [83]

Legend:
 Hg = mercury; met. = metallic (~Hg vapour), f = female, m = male, Y = years, M = months

The many cases of high exposure of children to methyl mercury (Minamata, Iraq, fish consumption) as documented in many studies give no indication of acrodynia having occurred. Nor are there any reports of cases of acrodynia in small children after use of thiomersal (ethyl mercury) in vaccines. Interestingly, only one case of acrodynia in persons over 18 years of age has been described to date; it was induced by thiomersal (mercury ethyl sodium thiosalicylate) in a 20-year-old patient who over a period of 15 years had been

treated regularly with injections of gamma globulin [24]. No cases of acrodynia in adults are known, despite extensive experience with occupational exposure to mercury vapour.

Since 1950, i.e. since the link between acrodynia and mercury became known, millions of children have received amalgam fillings. No cases of acrodynia in children with amalgam fillings have been described [25]. Two recent prospective studies in Lisbon and Boston each investigated over 500 children (aged six to ten years) for potential adverse effects over periods of, respectively, five and ten years after initial treatment with dental amalgam (medians of 16 and 14 years, respectively). The children had urinary mercury levels < 2 µg/g creatinine. No cases of acrodynia were described [26, 27]. Little else could be expected, given the rarity of the disease (1/500 or 1/1000) and the size of the study groups (500 children each).

The fact that only very few children contracted the disease from among a multitude of children with high exposure – whether via calomel-containing teething powder, calomel-containing “worm chocolate” or mercury-contaminated diapers – gave rise to the conclusion that those children were particularly sensitive. It is unclear what causes these differences in individual susceptibility and whether they are genetically determined. There is generally a need for research to establish what individuals are highly vulnerable [28]. The following has been discussed as a possible cause of greater susceptibility: metabolic disturbance of mercury excretion [29]; kinetic differences due to polymorphisms in the glutathione system [30, 31]; and polymorphisms of coproporphyrinogen oxidase and in Brain Derived Neurotrophic Factor (BDNF) [32, 33].

Acrodynia and measured Hg levels

In most of the acrodynia cases, mercury levels in blood and urine were above the HBM II values of, respectively, 15 µg/l blood and 20 µg/g creatinine or 25 µg/l urine, but 10 percent had levels below these values. With the exception of two children, mercury levels in urine were always above the HBM I level (5 µg/g creatinine or 7 µg/l). A sharp increase in Hg in urine was always observed after administration of a chelating agent. In the cases published by Chamberlain and Quilian in 1963 [13], four out of 19 children had urinary mercury levels below 10 µg/l. In this regard, it should be noted that in the cases described in the older literature, wet chemical analysis methods were used to determine Hg in body fluids. These methods were not sufficiently accurate and reliable, particularly at levels close to the detection limit, and there was hardly any external quality control in these analyses. Moreover, in most cases, no detailed information was given on the duration of exposure and on the time elapsed between exposure and the taking of samples for human biomonitoring. One reason

for this is the long and varied latency period of the disease and the resulting fact that it was often diagnosed at a late stage.

A relationship between dose and severity was not observed for idiosyncratic reactions to mercury compounds [34, 35]. Nevertheless, those cases where human biomonitoring was performed soon after exposure offer the Commission no convincing evidence that acrodynia occurs at exposure levels below the HBM I value. There is some evidence, however, that acrodynia may occur at exposure levels below the HBM II value.

In many of the published cases, only individual analyses for mercury were performed, and no differentiated biomonitoring analyses that would allow exposure over time and mercury burdens in urine and blood to be quantified and evaluated in connection with the occurrence of complaints.

Conclusions of the Commission

- Acrodynia is a rare disease that occurs in children and youths which requires clinical diagnosis on the basis of typical manifestations (**Overview 1**).
- In case of a clinical suspicion of acrodynia, analysis for mercury in urine (24 h sample if possible) and blood should be initiated immediately for confirmation.
- Potential sources should be identified and detailed information collected on exposure routes and exposure periods through targeted anamnesis.
- As well as elevated exposure to mercury compounds, individual susceptibility (“idiosyncratic reaction”) must be assumed to be a causative factor for acrodynia.
- Against this background, the Commission views the available data on acrodynia as presenting no basis for changing the HBM values. Genetically regulated, allergic and immunotoxic reactions to mercury are not subject to a dose-effect relationship for which a threshold value can be derived. Therefore, no limit values can be derived for mercury in the blood and urine of susceptible persons [36].
- The Commission cannot clearly exclude that manifestations of acrodynia could develop in susceptible persons even at low exposure levels (between HBM I and HBM II). Therefore, it is important that such cases be documented from the very beginning and in their further development through human biomonitoring and that potential causes of the idiosyncrasy be confirmed in further scientific work and published.

The HBM values for mercury (HBM I value: 5 µg/l blood, 7 µg/l urine or 5 µg/g creatinine in urine; HBM II value: 15 µg/l blood, 25 µg/l urine or 20 µg/g creatinine in urine) [1] agree well

with the evaluations of other organisations. For example, Health Canada has published a guidance value of 20 µg/l blood which should not be exceeded (Health Canada, as cited by [37]). The U.S. Environmental Protection Agency (EPA) [38]) and the National Academy of Sciences (NAS) [39] have confirmed a “reference dose” for methyl mercury of 0.1 µg/kg body weight and recommended that blood mercury levels should be below 5.0 µg/l and mercury levels in scalp hair below 1 µg/g. The current reference levels for mercury levels in the blood and urine of the German population are: Hg in whole blood of children (3 to 14 years of age) who eat fish up to three times per month: 0.8 µg/l; Hg in whole blood of adults (18 to 69 years of age) who eat fish up to three times per month: 2 µg/l; Hg in morning urine of children (3 to 14 years of age) without amalgam fillings: 0.4 µg/l; Hg in morning urine of adults (18 to 69 years of age) without amalgam fillings: 1 µg/l [40, 41]. They are thus well below the HBM values [1].

In the past, misunderstandings have arisen about the need for action when body levels exceed the reference value while remaining at the same time below the HBM I value. In its “Addendum to the concept of reference and human biomonitoring (HBM) values in environmental medicine” [42] and in the following, the Commission provides clarification on this point: In general, action is necessary from the human-medicine and toxicological point of view when the toxicologically derived HBM values are exceeded [42, 43]. Body levels below the HBM I value which at the same time exceed the current reference value constitute an exposure in excess of the background level. If such exposure to a toxic substance exists, it should be examined from the perspective of environmental hygiene and preventative medicine whether this exposure can be reduced with reasonable efforts, that is to say, whether conspicuous sources exist and are avoidable or whether some other explanation for this “uncommonly high” level can be found [42, 43].

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References

1. Kommission Human-Biomonitoring des Umweltbundesamtes (1999) Stoffmonographie Quecksilber – Referenz- und Human-Biomonitoring-(HBM)-Werte. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 42: 522-32

2. von Mühlendahl KE (2008) Die Feersche Krankheit (Akrodynie) – eine seltsame Krankheit. *Umweltmed Forsch Prax* 13: 73-79
3. Selter P (1903) Trophodermatoneurosis. *Arch f. Kinderh.* 37: 468f
4. Dally A (1997) The rise and fall of pink disease. *Social history of medicine* 10: 291-304
5. Bilderback JB (1925) Acrodynia. *JAMA* 84:495-498
6. Björklund G (1995) Mercury and acrodynia. *The Journal of Orthomolecular Medicine* 10 (2): 145-146
7. Black J (1999) The puzzle of pink disease. *J Royal Soc Med* 92: 478-81
8. Davis LE (2000) Unregulated potions still cause mercury poisoning. *West J Med* 173: 19
9. Warkany J, Hubbard DM (1948) Mercury in the urine of children with acrodynia. *Lancet*: 829-38
10. Logan WPD, (1949) Mortality from pink disease 1923-1947. *Lancet* 608-609
11. Warkany J (1966) [Acrodynia-postmortem of a disease](#). *Am J Dis Child.* 112: 147-56
12. Fanconi G, Botzstejn P, Schenker P (1947) Überempfindlichkeitsreaktionen auf Quecksilbermedikation im Kindesalter. *Helv paediat Acta (Suppl 4)* 2: 3ff
13. Chamberlain JL, Quillian W (1963). Acrodynia. A long-term study of 62 cases. *Clinical Pediatrics* 2: 439-443.
14. Gotelli CA, Astolfi E, Cox C, Cernichiari E, Clarkson TW (1985) Early biochemical effects of an organic mercury fungicide on infants: "dose makes the poison". *Science* 227: 638-40
15. Koh C, Kwong KL, Wong SN (2009) Mercury poisoning: a rare but treatable cause of failure to thrive and developmental regression in an infant. *Hong Kong Med J* 15: 61-64
16. van der Linde AA, Lewiszong-Ruthjens CA, Verrips A, Gerrits GP (2009) A previously healthy 11-year-old girl with behavioural disturbances, desquamation of the skin and loss of teeth. *Eur J Pediatr* 168:509-11
17. Zurek M, Tröger I, Richter T, Borte M (2008) Feersche Krankheit- einer Erkrankung der Vergangenheit? *Kinder-Jugendmedizin* 3/2008, V11
18. Radke M, Klinikum Ernst von Bergmann, Potsdam, 2009, persönliche Mitteilung
19. Henningsson C, Hoffmann S, McGonigle L, Winter JS (1993) Acute mercury poisoning (acrodynia) mimicking pheochromocytoma in an adolescent. *J Pediatr* 122: 252-3
20. Weinstein M, Bernstein S (2003) Pink ladies: mercury poisoning in twin girls. *Can Med Assoc* 168: 201
21. Zelman M, Carnfield P, Moss M, Carnfield C, Sweet L (1991) Toxicity from vacuumed mercury: A household hazard. *Clinical Pediatrics* 30: 121-123
22. Schwartz JG, Snider TE, Montiel MM (1992) Toxicity of a family from vacuumed mercury. *Amer J Emerg Med* 10: 258-261.
23. Eschenhagen P, Grimm T, Radke M (2005) Quecksilberintoxikation bei zwei 12 jährigen Mädchen. 56. Jahrestagung der NDGKJ, Berlin
24. Mathesen DS, Clarkson TW, Gelfand EW (1980) Mercury toxicity (acrodynia) induced by long term injection of gamma globulin. *J Pediatr* 97:153-155
25. von Mühlendahl (1995) Dental amalgam and Feer disease. *Eur J Pediatr* 154: 585-586
26. DeRouen TA, Martin MD, Lerroux BG et al. (2006) Neurobehavioural effects of dental amalgam in children: a randomized clinical trial. *JAMA* 295: 1785-1792
27. Bellinger DC, Trachtenberg F, Barregard et al. (2006) Neuropsychological and renal effects of dental amalgam in children: a randomized clinical trial. *JAMA* 295: 1775-1783
28. Needleman HL (2006) Mercury in Dental Amalgam – A neurotoxic risk? *JAMA* 295: 1835-1836.
29. Haley BE (2005) Mercury toxicity: Genetic susceptibility and synergistic effects. *Medical Veritas* 2: 535-542.

30. Custodio HM, Broberg K, Wennberg M, Jansson JH, Vessby B, Hallmans G (2004) Polymorphisms in glutathione-related genes affect methylmercury retention, *Arch Environ Health* 59: 588-595.
31. Schläwicke Engström K, Strömberg U, Lundh T, Johansson I, Vessby B, Hallmans G, Skerfving S, Broberg K (2008) Genetic Variation in Glutathione-Related Genes and Body Burden of Methylmercury, *Environ Health Perspect* 116: 734-739
32. Echeverria D, Woods JS, Heyer NJ, Rohlman DS, Farin FM, Bittner AC Jr, Li T, Garabedian C (2005) Chronic low-level mercury exposure, BDNF polymorphism, and associations with cognitive and motor function. *Neurotoxicol Teratol* 27: 781-796
33. Woods JS, Echeverria D, Heyer NJ, Simmonds PL, Wilkerson J, Farin FM (2005) The association between genetic polymorphisms of coproporphyrinogen oxidase and an atypical porphyrinogenic response to mercury exposure in humans. *Toxicol Appl Pharmacol* 206:113-120
34. Magos L, Clarkson TW (2006) Overview of the clinical toxicity of mercury. *Ann Clin Biochem* 43: 257-68
35. WHO (1991) Inorganic mercury. *Environ Health Crit* 118: 98-99
36. Kazantzis G (2002) Mercury exposure and early effects: an overview. *Med Lav* 93: 139-47
37. Wong SL, Lye EJD (2008) Lead, mercury and cadmium levels in Canadians. *Statistics Canada* no. 82-003-XPE. Health reports, Vol. 19, no. 4 December 2008.
38. Environmental Protection Agency (1998) Office of Air Quality Planning and Standards. Mercury Study Report to Congress. *Govt Reports Announcements and Index (GRA and I)*, Issue 09, available: <http://www.epa.gov/mercury/report.htm>
39. NAS. July 2000. Toxicological Effects of Methylmercury. Washington, DC:National Academy of Sciences. available: <http://nap.edu/books/0309071402/html>
40. Kommission Human-Biomonitoring des Umweltbundesamtes(2003) Aktualisierung der Referenzwerte für Blei, Cadmium und Quecksilber im Blut und Urin von Erwachsenen. *Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz* 46: 1112-1113
41. Schulz C, Angerer J, Ewers U, Heudorf U, Wilhelm M on behalf of the Human Biomonitoring Commission of the German Federal Environment Agency (2009) Revised and new reference values for environmental pollutants in urine or blood of children in Germany derived from the German Environmental Survey on Children 2003-2006 (GerES IV). *Int. J. Hyg. Environ. Health* 212, doi:10.1016/j.ijheh.2009.05.003, available: <http://www.elsevier.de/intjhyg>
42. Kommission Human-Biomonitoring des Umweltbundesamtes (2009) Addendum zum Konzept der Referenz- und Human-Biomonitoring-Werte (HBM) in der Umweltmedizin. *Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz* 52 (8):874-877
43. Kommission Human-Biomonitoring des Umweltbundesamtes (1996) Konzept der Referenz- und Human-Biomonitoring (HBM)-Werte in der Umweltmedizin. *Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz* 39: 221-224.
44. Chrysochoou C, Rutishauser C, Rauber-Lüthy C, Neuhaus T, Boltshauser E Superti-Furga A (2003) An 11-month-old boy with psychomotor regression and auto-aggressive behaviour. *Eur J Pediatr* 162: 559-61
45. Cloarec S, Deschênes G, Sagnier M, Rolland JC, Nivet H (1995) Arterial hypertension due to mercury poisoning: diagnostic value of captopril. *Arch Pediatr* 2: 43-6
46. Velzeboer SCJM, Frenkel J, de Wolff FA (1997) A hypertensive toddler. *Lancet* 349: 1810,
47. von Mühlendahl (1990) Intoxication from mercury spilled on carpets. *Lancet* 336: 1578
48. Koyun M, Akman S, Gür Güven A (2004) Mercury intoxication resulting from school barometers in three unrelated adolescents. *Eur J Pediatr* 163: 131-34
49. Beck C, Krafchik B, Traubici J, Jacobson S (2004) Mercury intoxication: It still exists. *Pediatr Dermatol* 21: 254-59

50. Gattineni J, Weiser S, Becker AM, Baum M (2007) Mercury intoxication: Lack of correlation between symptoms and levels. *Clin Pediatr* 46: 844-46
51. Abbaslou P, Zaman T (2006) A child with elemental poisoning and unusual brain MRI findings. *Clin Toxicol* 44: 85-88
52. Dinehart SM, Dillard R, Raimer SS, Diven S, Cobos R, Pupo R (1988) Cutaneous manifestations of acro-dynia. *Arch Dermatol* 124: 107-9
53. Michaeli-Yossef Y, Berkovitch M, Goldman M (2007) Mercury intoxication in a 2-year-old girl: a diagnostic challenge for a physician. *Pediatr Nephrol* 22: 903-6
54. Agocs MM, Etzel RA, Parrish RG, Paschal DC, Campagna PR, Cohen DS, Kilbourne EM, Hesse JL (1990) Mercury exposure from interior latex paint. *N Engl J Med* 323: 1096-1101
55. CDC (1990) Mercury exposure from interior latex paint. *MMWR* 39: 125-6
56. Hertl M, Rösiger A, Schultze-Rhonhof J, Schweinsberg H-W (1982) Akro-dynie (Feer-Krankheit). *Der Kinderarzt* 13: 677-81
57. Swaiman KF, Flagler DG (1971) Mercury poisoning with central and peripheral nervous system involvement treated with penicillamine. *Pediatrics* 48: 639-42
58. Curtis HA, Ferguson SD, Kell RL, Samuel AH (1987) Mercury as a health hazard. *Arch Dis Child*, 62: 293-295
59. Tunnessen WW, McMahon KJ, Baser M (1987) Acro-dynia: Exposure to mercury from fluorescent light bulbs. *Pediatrics* 79: 786-9
60. Hirschman SZ, Feingold M, Boylen G (1963) Mercury in house paint as a cause of acro-dynia. *N Engl J Med* 269: 889-93
61. Shih H, Gartner JC jun (2001) Weight loss, hypertension, weakness, and limb pain in a 11 year old boy. *J Pediatr* 138: 566-9
62. Karpathios T, Zervoudakis A, Theodoridis C, Vlachos P, Apostolopoulou E, Fretzayas A (1991) Mercury Vapour poisoning associated with hyperthyroidism in a child. *Acta Pediatr Scand* 80: 551-2
63. Horowitz Y, Greenberg D, Ling G, Lifshitz M (2002) Acro-dynia: a case report of two siblings. *Arch Dis Childhood* 86: 453
64. Borth-Bruns T, Sauer S, Hofbeck M, Schweinsberg (2003) Klinisches Bild, diagnostische Vorgehensstrategie und Behandlung bei einem Fall von Quecksilbervergiftung im Kindesalter. *Umweltmed Forsch Prax* 8: 206
65. de Oliveira JJ, Silva SR (1996) Arterial hypertension due to mercury intoxication with clinical and laboratorial syndrome simulating pheochromocytoma. *J Pediatr* 72: 40-3,
66. Wößmann W, Kohl M, Grüning G, Bucsky (1999) Mercury intoxication presenting with hypertension and tachycardia. *Arch Med Child* 80: 556-7
67. Foulds DM, Copeland KC, Franks RC (1987) Mercury poisoning and acro-dynia. *Am J Dis Child* 141: 124-5
68. Alexander JF, Rosario R (1971) A case of mercury poisoning: acro-dynia in a child of 8. *CMA J* 104: 929-930
69. Tominack R, Weber J, Blume C, Madhok M, Murphy T, Thompson M (2002) Elemental mercury as an attractive nuisance: Multiple exposures from a pilfered school supply with severe consequences. *Pediatr Emergency Care* 18: 97-100
70. Böckers M, Schönberger W, Oster O, Neumann P (1983) Inhalative Quecksilbervergiftung unter dem klinischen Bild einer Acro-dynie (Selter-Swift-Feer). *Dtsch med. Wschr* 108: 825-828.
71. Torres AD, Rai AN, Hardiek ML (2000) Mercury intoxication and arterial hypertension: Report of two patients and review of the literature. *Pediatrics* 105: e34
72. Laurans M, Brouard J, Arion A, Kauffmann D, Duhamel JF (2001) Familial mercury intoxication presenting with cardiovascular abnormalities and acro-dynia. *Acta Pediatr* 90: 593-4

73. McNeil NI, Olver RE, Issler RE, Wrong OM (1984) Domestic metallic mercury poisoning. *Lancet* 269-71
74. Rennie AC, McGregor-Schuerman M, Dale IM, Robinson C, McWilliam R (1999) Mercury poisoning after spillage at home from a sphygmomanometer on loan from hospital. *Brit Med J* 319:366-7
75. Baughman TA (2006) Elemental mercury spills. *Environ Health Perspect* 114: 147-52
76. Yeates KO, Mortensen ME (1994) Acute and chronic neuropsychological consequences of mercury vapour poisoning in two early adolescents. *J Clin Exp Neuropsychol* 16: 209-22
77. CDC (1990) Epidemiologic notes and reports elemental mercury poisoning in a household – Ohio 1989. *MMWR* 39: 424-5
78. Sexton DJ, Powell KE, Liddle J, Smrek A, Smith JC, Clarkson TW (1978) A nonoccupational outbreak of inorganic mercury vapour poisoning. *Arch Environ Health* 33: 186-91
79. George EA, Sarojini PA (1993) Case Report: Acrodynia. *Ind J Dermatol Venereol Leprol* 59: 77-79
80. Fayez I, Paiva M, Thompson M, Verjee Z, Koren G (2005) Toxicokinetics of mercury elimination by dimercaptosuccinic acid in twin toddlers. *Pediatr Drugs* 7: 397-400
81. MacLehose R, Pitt G, Will S, Jones A, Duane L, Flaherty S, Hannant D, Stuttard B, Silverwood A, Snee K, Murray V, Syed Q, House I, Bellis MA (2001) Mercury contamination incident. *J Publ Health Med* 23: 18-22
82. Bonhomme C, Gladyszaczak-Kholer J, Cadou A, Illef D, Kadi Z (1996) Mercury poisoning by vacuum-cleaner aerosol. *Lancet* 347: 115
83. Cherry D, Lowry L, Velez L, Cotrell C, Keyes DC (2002) Elemental mercury poisoning in a family of seven. *Fam Commun Health* 24: 1-8