HEALTH EFFECTS FROM EXPOSURE TO CHRONIC LEVELS OF INDUSTRIAL CHEMICALS

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Summary

Chronic health effects on workers are usually caused by repeated exposure to industrial chemicals for a long time at rather low concentrations in the workplace. There is no clear definition about chronic occupational poisoning. Definition of chronic occupational toxicity is introduced from the viewpoint of the ACGIH (American Conference of Governmental Industrial Hygienists) and the JSOH (Japan Society For Occupational Health). Industrial chemicals have some specific or major toxicity with other minor toxicity.

Important, specific, or major toxicity such as neurotoxicity, reproductive toxicity, carcinogenicity, and immunotoxicity of chemicals are described, and industrial chemicals classified by specific toxicity are listed in the tables. Cases of chronic occupational poisoning such as n-hexane polyneuropathy, reproductive disorders due to 2-bromopropane, and leukemia associated to benzene are described as examples to understand health effects from exposure to chronic levels of industrial chemicals. The hygienic standards for industrial chemicals and viewpoints of the ACGIH and JSOH are described. Finally, important issues in extrapolation from data of animal experiments to

humans are described.

1. Definition of Chronic Toxicity

Chronic health effects on workers are usually caused by repeated exposure of industrial chemicals for a long time at rather low concentrations in the workplace. There is no clear definition about chronic poisoning in terms of exposure period. Usually, health effects of acute poisoning are considered due to less than 5–15 minutes exposure of high concentration such as irritation and narcosis, etc. Sub-chronic poisoning is a rather specific health disorder due to moderate levels of exposure for less than 3–6 months. Chronic poisoning is a health disorder due to low levels of exposure for more than 3–6 months, which sometimes include aftereffects of acute and sub-chronic poisoning, malignant tumors occurring many years after exposure, effects on the following generations, shortening of life span and etc. Generally speaking, chronic poisoning could cause less specific health disorders than a sub-chronic one. Ambient concentrations in the workplace usually fluctuate in a wide range during working hours, day-by-day, and year-by-year. Workers are working 6–8 hours a day, 5–6 days a week, for about 40–45 years, from starting of work to retirement. Therefore, the health disorders caused by occupational exposure from 3–6 months to 40–45 years could be regarded as chronic poisoning. However, accurate assessment of long-term exposure might be very difficult because sufficient data of exposure levels are not available in most cases.

2. Specific Toxicity or Target Organs of Chemicals

Industrial chemicals have one or more specific or major toxicity with minor toxicity, respectively. Some organs are specifically susceptible to some chemicals. For example, carbon tetrachloride is specifically toxic to the liver, cadmium is toxic to the kidney, benzene is toxic to the haematopoietic organs, n-hexane is toxic to the peripheral nerve, 2-bromopropane is toxic to the reproductive organs, benzene is an agent linked to causes of leukemia, toluenediisocyanate (TDI) is an allergen to cause asthma, and so on. The specific or major toxicity is important to detect early signs of health disorders, and establish the threshold limit values of chemicals to prevent the occupational poisoning, because it is the most sensitive parameters for toxicity of chemicals. However, it should be noted that industrial chemicals have other toxicity apart from major toxicity. Important specific or major toxicity such as neurotoxicity, reproductive toxicity, carcinogenicity, and immunotoxicity of industrial chemicals are described in the following section, and industrial chemicals classified by specific or major toxicity are listed in the tables.

2.2. Neurotoxicity

Neurotoxicity is any effects on the structure or function of the central and/or peripheral nervous system related to exposure of a chemical substance. Recently, neurotoxicity has become an important endpoint in hazard identification and assessing the risks of chemicals. The nervous system is of particular interest because mature neurons are generally incapable of regeneration. The disorders of the nervous system due to chronic exposure to industrial chemicals are usually very hard to recover, and sometimes tend to

become gradually more serious even after removal from the exposure. In addition, the normal cascade of brain development during fetal and newborn life may be exquisitely sensitive to disruption by chemicals, resulting in lasting and profound nervous system dysfunction. Human exposure to potential neurotoxic substances is increasing public concern. Main neurotoxic chemicals to which workers may be exposed in the workplace are listed in the table (see Table 1).

Chemicals	**Chemicals**
Acrylamide	Mercury, inorganic
Alkanes	Methyl alcohol
Anesthetic gases, waste	Methyl parathion
Carbaryl	Methyl chloride
Carbon disulfide	Nitriles
Carbon monoxide	Parathian
Carbon tetrachloride	Petroleum solvents, refined
Chloroform	Styrene
Cresol	1, 1, 2, 2-Tetrachloroethane
Dinitro-o-cresol	Tetrachloroethylene
Ethylene dibromide	Thiols
Fluorocarbon polymers, decomposition products	Toluene
Formaldehyde	1, 1, 1-Trichloroethane
Hydrogen cyanide and salts	Tungsten and cemented tungsten products
Hydrogen sulfide	Xylene
Ketones	Zinc oxide
Lead, inorganic/organic	
Malathion	

Table 1. Chemicals producing neurotoxic effects at low concentrations.

2.3. Reproductive Toxicity

Reproductive toxicity encompasses adverse health effects in the prospective mother, the father, the developing embryo, and infant. The most striking features of reproduction are the myriad of rapid multiplying cells in the ovary, testis, or tissues of the embryo, and such cells to various chemicals would be much more susceptible than would be anticipated to elicit toxicity in other cell systems at low concentration. In reproductive toxicology, it is insufficient to determine that the target site of the agent is the testis, the ovary, and the conception, etc. The various direct and indirect events occurring during

the reproductive–development cycle, each of these being characterized by multiple components should be examined. Information about reproductive toxicity of industrial chemicals is very limited as yet. Main well-known reproductive toxicants in the workplace are listed in the table (see Table 2).

Chemicals associated with male	**Chemicals associated with female**
Boron	Aromatic hydrocarbons (e.g. toluene)
Benzene	2-Bromopropane
2-Bromopropane	Cadmium
Cadmium	Carbon monoxide
Carbon disulfide	Carbon disulfide
Carbon monoxide	Cytostatic drugs
Carbon tetrachloride	Dibromochloropropane (DBCP)
Carbaryl	Ethylene glycol
Chlordecone	Ethylene oxide
Chloroprene	Halogenated anesthetic gases
Dibromochloropropane (DBCP)	Lead
Dimethyl dichlorovinyl phosphate (DDVP)	Mercury
Epichlorohydrin	Nitrous oxide
Estrogens	Manganese
Ethylene oxide	Ozone
Ethylene dibromide (EDB)	Polybrominated biphenyls (PBBs)
Ethylene glycol ethers	Polystyrene
Lead	Polychlorinated biphenyls (PCBs)
Manganese	Polyurethane
Polybrominated biphenyls (PBBs)	Styrene
Polychlorinated biphenyls (PCBs)	

Table 2. Chemicals associated with reproductive disorders.

2.4. Carcinogenicity of Chemicals

Cancer ranks as the toxic effects of most concern to the public. Because of this, considerable effort and financial resources are spent annually to identify potential human carcinogens. ACGIH (American Conference of Governmental Industrial Hygienists) classifies occupational carcinogens into A1 to A5. A1 is a confirmed human carcinogen including 18 chemicals. A2 is a suspected human carcinogen including 25

chemicals. A3 is a confirmed animal carcinogen including 83 chemicals. A4 is not classifiable as a human carcinogen including 83 chemicals. A5 is not suspected as a human carcinogen including 2 chemicals. JSOH (Japan Society for Occupational Health) classifies occupational carcinogens into group 1, group 2A, Group 2B according to the criteria of International Agency for Research on Cancer (IARC). Group 1 includes 20 chemicals that are carcinogenic to humans. Group 2A includes 20 chemicals that are probably carcinogenic to humans having more sufficient evidence. Group 2 B includes 103 chemicals that are possibly carcinogenic to humans having less sufficient evidence. Industrial chemicals classified into Group 1 and Group 2A by JSOH are listed in the table (see Table 3).

Group 1 (carcinogenic to humans)	**Group 2A (probably carcinogenic to humans)**
4-Aminophenyl	Acrylonitrile
Arsenic and compounds	Acrylamide
Asbestos	Benzo [a] pyrene
Benzene	Beryllium and compounds
Benzidine	1, 3-Butadiene
Benzotrichloride	Chloromethyl methyl ether (technical grade)
Bis (chloromethyl) ether	Creosotes
Cadmium and compounds	3, 3'-Dichloro-4, 4'-diaminodiphenylmethane
Chromium (VI) compounds	(MBOCA)
Coal-tar pitches	Diethyl sulphate
Coal-tars	Dimethyl sulphate
Erionite	Dimethylcarbamoyl chloride
Ethylene oxide	Epichlorohydrin
Mineral oils (untreated and mildly treated)	Formaldehyde
2-Naphthylamine	P-Chloro-o-toluidine and its strong acid salts
Nickel compounds (except Ni metal)	Polychlorinated biphenyl (PCB)
Soots	Silica (crystalline)
Sulphur dichlordiethyl	Styrene oxide
Talc containing asbestiform fibers	Tris phosphate (2, 3-dibromopropyl)
Vinyl chloride	Vinyl bromide
Wood dust	Vinyl fluoride

Table 3. Occupational carcinogens.

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Bibliography

ACGIH (1999). Threshold limit values for chemical substances and physical agents, *Biological Exposure Indices 1999*. Cincinnati: ACGIH. [This recommends threshold limits values of many chemicals in the workplace.]

Ellenhorn M. J. (1997). Principles of poison management; the pregnant patient. *Ellenhorn's Medical Toxicology* 2nd Ed. pp. 149–171. Baltimore: Williams and Wilkins. [This presents reproductive toxicity of many chemicals and their classification based on human and animal evidence.]

JSOH (1999). Recommendation of Occupational Exposure Limits (1999–2000). *Journal of Occupational Health* **41**, 191–206. [This recommends occupational exposure limits of many chemicals in Japan.]

Kaneko T., Wang P. T., and Sato A. (1997). Benzene-Associated Leukemia and its Risk Assessment. *Journal of Occupational Health* **39**, 159–178. [This presents a comprehensive risk-assessment of benzene exposure in the workplace.]

Koh J. M., Kim C. H., Hong S. K., Lee K. U., Kim Y. T., Kim O. J., and Kim G. S. (1998). Primary Ovarian Failure Caused by a Solvent Containing 2-Bromopropane. *European Journal of Endocrinology* **138**, 554–556. [This presents 2 years follow-up study on the patients with amenorrea caused by 2-bromopropane exposures in Korea.]

Schulze G. E. (1995). *Neurotoxicity*. CRC Handbook of Toxicology (eds. Derelanko M. D. and Hollinger M. A.) pp. 277–292. New York: CRC press. [This presents a comprehensive description on neurotoxicity of many chemicals.]

Takeuchi Y., Ono Y., Hisanaga N., Kitoh J., and Sugiura Y. (1980). A Comparative Study on the Neurotoxicity of N-Pentane, N-Hexane, and N-Heptane in the Rat. *British Journal of Industrial Medicine* **37**, 241–247. [This presents specific neurotoxicity of n-hexane compared with n-pentane and heptane in rats.]

Takeuchi Y., Ichihara G., and Shibata E. (1997a). Modification of Hexane Neurotoxicity by Other Organic Solvents, its Mechanism, and Risk Assessment. *Advances in Occupational Medicine and Rehabilitation* **3**(3), 225–232. [This presents dose-response relationship of n-hexane polyneuropathy occurred in vinyl sandal manufacturers in Japan.]

Takeuchi Y., Ichihara G., and Kamijima M. (1997b). A Review on Toxicity of 2-Bromopropane: Mainly on its Reproductive Toxicity. *Journal of Occupational Health* **39**, 179–191. [This presents the reproductive toxicity of 2-bromopropane based on the cases of workers and the results of animal experiments.]

Thomas P., and House R. V. (1995). *Pre-clinical Immunotoxicity Assessment*. CRC Handbook of Toxicology (eds. Derelanko M. D. and Hollinger M. A) pp. 293–316. New York: CRC press. [This presents immunotoxicity assessment of many chemicals.]

Biographical Sketch

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