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Occupational exposure to neurotoxic substances in Asian countries - Challenges and approaches

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Abstract

The fact that a conference on neurotoxicity was held in China triggered the idea to provide an insight into occupational diseases, their development and the approaches to investigate them in Asian countries. A historical review, a meta-analysis, and studies on humans and animals provide impressions on past and current problems.

The Korean example showed that each newly introduced industry is accompanied by its own problems as regards occupational diseases. Mercury and carbon disulfide were of importance in the beginning, whereas solvents and manganese became important later. Outbreaks of diseases were important reasons to guide both the public and the governmental attention to prevention and allowed within a relatively short time considerable progress. As the example on the replacement of 2-bromopropane by 1-bromopropane showed, also the introduction of chemicals that are more beneficial for the environment may result in additional occupational risks. A lower mutagenicity of 1-bromopopane was shown to be associated with a greater neurotoxicity in Japanese studies. Although occupational health and diseases are commonly related to adults, child workers exposed to solvents were examined in a Lebanese study. The study started outlining the health hazards in young workers because they might be at a much greater risk due to the not yet completed maturation of their nervous system. That some occupational diseases are not yet a focus of prevention was shown by the study on pesticides. If at all, the serious health consequences resulting from excessive exposure were investigated. Research enabling precautionary actions was not available from the international literature.

Despite globalization the knowledge on occupational diseases is not yet “globalized” and each country obviously undergoes its own development triggered by local experiences. Economic development that requires a healthy workforce, but also public interest that challenges governmental regulations further efforts on the prevention of occupational diseases.

The paper reflects a summary of the talks presented at the symposium “Occupational Neurotoxicities in Asian Countries” as part of the 11th International Symposium on Neurobehavioral Methods and Effects in Occupational and Environmental Health.

Keywords

Neurobehavioral Toxicology; Neuropsychological Tests; Occupational Disease; 1-Bromopropane; Working Children; Pesticides; Manganese

1. Introduction

Asian countries are far from being a homogenous entity; too different are their cultural backgrounds and their stages of economic and industrial development. A neurotoxicological conference held in China was the reason to provide insights into topics, developments, stages, and shortcomings of the current research.

Asia is a region that has experienced considerable industrial and economic development during the last decades. The pace and the level reached, however, are very different in the individual countries. Nevertheless, neurotoxic effects on human health are of importance at each state. While pesticides may put the workers' health at risk in more agricultural countries, the industrialized countries may face greater problems from the exposure to solvents or metals for example. It may be of interest to have a look at the forces that drive the detection and prevention of neurological diseases. Which diseases gain interest? Which events trigger regulations? Which regulations get implemented? In which way does this process alter diseases? Which lessons had/have to be learned?

Some of these questions will be addressed by the summary on "Occupational neurotoxicity in Korea". It gives an example which neurological diseases might occur and how a regulatory system changes when a country undergoes a rapid industrialization.

Industry does not yet have a leading role in all Asian countries; therefore agriculture remains an important sector. The need to feed an increasing population may increase the use of pesticides and occupational health should also focus the agricultural sector. However, small scale farming, migrant workers, illiteracy, child labor, and a biomarker like erythrocyte AChE that is not adequate for the measurement of lower exposures (He, 1999) do not facilitate the research on pesticides. The summary on "The impact of occupational exposure to pesticides" sought to review the Asian contributions to the understanding of the neurobehavioral impact of pesticides.

Although many of the industrialized countries implemented regulations on child work that preclude children - usually under the age of 16 - from working on a regular basis, child labor remains a topic in many regions of the world. Millions of children work in hazardous conditions and are exposed to pesticides and other chemicals. The UNICEF (United Nations International Children's Emergency Fund) estimates that only in South Asia about 44 million children are engaged in child labor (UNICEF, 2011). The outline on "Solvent neurotoxicity among working children in Lebanon" describes one of the studies that tries to assess the health risk for some of these children.

Environmental concerns and/or human health effects sometimes trigger the abandoning of chemicals and their substitution. The ban on the use of DDT in 1972 (U. S. Environmental Protection Agency, 1975) is probably a well-known example all over the world. The summary on "Neurotoxicity of 1-bromopropane, an alternative to ozone-depleting solvents" reports experiences with the replacement of substances and the emerging problems. It further provides a rationale for the implementation of an occupational exposure level.

2. Occupational neurotoxicity in Korea: history of occupational neurological disorders

At the beginning of the last century, Korea was still a predominantly agricultural country with more than half of the economic active population employed in the agricultural sector. The industrialization started in the 1960s and since 1970 employment in the manufacturing industry rose to 36% of the working population; the major part of which was found in the textile, shoe and rubber industries. Heavy industries became an important part since the 1980s.

The industrialization introduced various kinds of chemicals (Kang and Kim, 2010) and as a consequence of the use of neurotoxic substances neurological disorders became important during the last three decades. The review seeks to outline the development of the diseases in the historical context and to delineate the events that contributed to changes and improvements in the prevention of occupational neurological diseases.

2.1. Methods

We reviewed the published literature regarding occupational neurological disorders in Korea between 1992 and 2009. The investigations we refer to were undertaken by the Occupational Safety and Health Research Institute of Korean Occupational Safety and Health Agency.

2.2. Results

Although agriculture was the largest part of the Korean economy until the 1960s and pesticides had been introduced in the 1950s, agriculture was not an industrialized sector in Korea. Most of the workers were self employed and run a family business. Only some of the pesticide workers were employed by fumigation companies in the industrial sector. They used methyl bromide for the fumigation of agricultural stocks. Until 2008, not more than 10 cases of severe methyl bromide intoxication were reported.

Since 1985, the acute neurotoxicity due to high exposure of chemicals became a problem. There were two important outbreaks of occupational neurological disorders in Korea. One of them resulted from intoxication by inorganic mercury and one from carbon disulfide.

Reports on inorganic mercury intoxication in Korea began in 1985 when a woman employed at a thermometer manufacturer was diagnosed as having an organic mental disorder (Jeong et al., 1985). In 1987, an epidemic from a fluorescent lamp manufacturer occurred when 18 out of the 25 workers at the manufacturer were tested for more than 0.03 μg/ml of serum mercury concentration (Hong et al., 1988). At this factory, four cases of chronic mercury poisoning were reported (Kim et al., 1988). In June 1988, a 15-year-old boy died, who had worked for 2 months in a company manufacturing precision instruments (Park et al., 1991).

Carbon disulfide intoxication was diagnosed in 1981 for the first time (Park and Kim, 1998). In 1987, more employees who had worked for the previous 10 years in the spinning process, making artificial silk thread from pulp dissolved in a carbon disulfide solution, were diagnosed with carbon disulfide poisoning, turning into an outbreak that numbered a total of 950 victims by 2008 (Kim, 2010). This company was built by used machines imported from a rayon company in Japan and started its operation in 1966. One study that evaluated the ex-employees of this rayon manufacturer reported that 61.5% of the workers had neurological disorders and 15.4% psychiatric disorders among the 117 chronic carbon disulfide poisoning patients (Kim et al., 1997).

After these incidents the government conducted an extensive survey on the mercury-using industry. Additionally, the regulation on occupational safety and health was amended; the work environment measurement system was introduced and labor inspection was enforced.

In the 1990s, chronic toxic encephalopathy and peripheral neuropathy raised public concerns. Most of the peripheral nervous system disorders were n-hexane-induced peripheral neuropathies reported from the electronics industry. Fifteen cases were reported by 2009 (Kim and Kang, 2010) and all but one were reported from workers employed by an LCD-frame and a cellular phone manufacturer.

Chronic toxic encephalopathy caused by mixed solvents was reported in 10 cases, including 3 female and 7 male workers (Kim and Kang, 2010). All patients had been exposed to mixed solvents. However, for some of them, toluene and trichloroethylene were the main components. Out of 10 cases, 4 patients could be classified as International Solvent Workshop (ISW) category 3, and 2 patients could be classified as ISW category 2B.

Reports of neuro-degenerative disease increased in the late 1990s. The first report of manganese (Mn) poisoning came from a welding rods manufacturer crushing ferromanganese in 1991 (Lim et al., 1991). After this report, most of the Mn-induced Parkinsonism cases in Korea were found in welders (Kim and Kang, 2010). In 1998, three welders with more than 10 years of welding experience were diagnosed with Mn-induced Parkinsonism. Their brain MRI showed high signal intensity in the basal ganglia on T1-weighted image. After this report, the Korea Occupational Safety and Health Agency (KOSHA) conducted an epidemiological study to clarify the clinical significance of increased signal intensities on T1-weighted MRI. During this study, the Occupational Safety and Health Research Institute did not discover any Parkinsonism or severely neurologically disabled cases out of the total subjects, but 73.5% of the welders showed increased signal intensities. Because these intensities were not correlated with neurological lesions, the study concluded that high signals of brain MRI did not necessarily indicate Mn-induced Parkinsonism, even if the patient had recent exposure to Mn (Kim et al., 1999). By 2008, 8 cases of Mn-induced neurological disorders had been reported, including three workers from a welding rod manufacturer, 4 welders and 1 painter (Kim and Kang, 2010). Further evaluations of brain imaging techniques for Mn neurotoxicity, such as H1 magnetic resonance spectroscopy (MRS) in welders, were conducted until 2007 (Kim and Kang, 2010).

Since the late 2000s, neurological disorders from long term, low level exposure became a major topic because protective measures against chemical exposures in the workplace had been introduced and the working environment improved continuously. With the aim of detecting earlier changes in neurological functioning in the workers who were exposed to neurotoxic chemicals, several studies have been conducted since the early 1990s. Since 1993, the WHO-NCTB was introduced into occupational studies on the neurotoxicity of mixed solvents to determine the applicability of the tool (Kang et al., 1993). Since 1994, a computerized tool developed by Korean researchers was used instead of the WHO-NCTB. This computerized test battery, called the Korean computerized neurobehavioral system (KCN), acquired validity and reliability through verification and tested intercultural as well as differences between computerized and non-computerized tests (Sakong et al., 2007). The Behavioral Assessment and Research System (BARS) was also translated into Korean and used for epidemiologic studies (Kang et al., 2005; Rohlman et al., 2003).

2.3. Discussion

Due to low numbers of reported cases in Korea, pesticide intoxication was not regarded as an occupational health concern. But, the research on occupational neurological disorders gained momentum after severe poisonings in other industries in the late 1980s. Particularly, the outbreak of carbon disulfide intoxication was of importance in the history of occupational disorders in Korea (Kim, 2010). The incidents had substantial influence on the occupational safety and health management system in Korea. As the neurological system is one of the major target organs of carbon disulfide and inorganic mercury, many researchers became interested in occupational neurotoxic disorders. After the carbon disulfide outbreak, the Korean government paid more attention to the development of a legal system of occupational safety and health as well as on a chemical management system such as the material safety data sheets (MSDS) system in workplaces (Hong et al., 1988). Nowadays, high exposure to organic solvents, including n-hexane, is not common, due to workplace improvements in Korea, including the reinforcement of the legal system in occupational safety and health. Thus, cases of classical chronic toxic encephalopathy with high exposure of organic solvents are rarely found any longer.

Many chemical industries were transferred from developed countries to Asian countries and carbon disulfide intoxication around the world might be a classical example. Carbon disulfide was a well known neurotoxic chemical earlier in the 19th century in Germany, from where it was transferred to other parts of Europe, USA and Japan and again transferred from those countries to less developed countries (Blanc, 2006). Japan reported the first victim in 1929. In the late 1960s, rayon factories from Japan were transferred to Korea and Taiwan, where they caused numerous intoxications. Therefore, one of the essential requirements for the effective prevention of neurotoxic disorders would be the international collaboration and exchange of the experience.

3. The impact of occupational exposure to pesticides – State of the art in Asian countries

There is no doubt about the severe neurological consequences of excessive exposure to pesticides (Alavanja et al., 2004; Keifer and Firestone, 2007; Lotti and Moretto, 2005), but whether chronic exposure in the absence of poisonings exerts significant effects on behavior, is less unequivocal and remains a matter of debate (Colosio et al., 2003; McCauley et al., 2006; Moser, 2007). Although the stage of industrialization is quite different in Asian countries, it can be assumed that pesticides are of importance also in Asia. China for example provides the greatest share of cotton in the world, Thailand is among the greatest exporters of rice and Asia has to feed 60% of the world's population. The conference on neurotoxicology held in Asia triggered the idea to quantify by means of a meta-analysis the evidence from Asian countries on effects of the occupational long-term exposure to pesticides. Neurobehavioral effects measured by neuropsychological tests should be analyzed.

3.1. Methods

In order to enable a meta-analysis on occupational exposure to pesticides we considered the following criteria as indispensible:

1. Random samples of exposed and unexposed participants
2. Neuropsychological tests employed in at least 3 different studies
3. Means and standard deviations of performance scores presented

Effect sizes calculated from the individual studies might then be used to estimate an overall effect by means of a random-effects model. The estimate of exposure-effect relationships would additionally require a measure of internal or external exposure.

In order to find the relevant articles, bibliographic searches were electronically conducted using the search terms "pesticide" or "organophosph*" or "carbamate" or "insecticide" and "occupational exposure", "neurobehavio*" and "psychol*". The results were restricted to articles in English, French or German. Data bases used were PubMed (National Library of Medicine), Science Direct (Elsevier,) Web of Science (ISI, Institute for Scientific Information), and Scopus (SciVerse Scopus, bibliographic database and citations for scholarly journal articles published by ELSEVIER since 2004). Additionally, the reference lists of reports were back-searched.

3.2. Results

One single study meeting the above mentioned minimal requirements was found. The study was conducted by Srivastava et al. in India and published in 2000 (Srivastava et al., 2000). Fifty-nine active workers manufacturing quinalphos were examined and the 3 employed performance tests showed significant lower performances on memory and attention in the exposed workers. The symptom scores were comparable in both groups.

Beyond that our search ascertained 8 studies from Asian countries that measured self-reported symptoms in persons exposed to pesticides, predominantly organophosphates. The majority of the examined persons had been occupationally exposed. The studies are shown in table 1 and grouped according to the share of poisoned subjects examined. In the upper part there are studies where the majority of participants suffered from an acute or recent poisoning. In the middle part there are studies that examined active workers, but did not specifically address poisonings. This probably indicates that they did at least not suffer from an acute poisoning; there may have been milder poisonings in the past. In the lower part of the table those studies are given in which hardly any participant suffered from poisonings at any time. Data are displayed on symptoms that were retrieved in most of the studies.

The comparison of the symptom shares shows that a symptom like nausea for example is much more prominent in the upper group of studies (60%, 73%, 92%) than in the middle (11%, 15%) or in the lower (8%). Similar trends can be seen for other symptoms.

3.3. Discussion

At least from the international literature is seems that occupational exposure to pesticides is not a well investigated topic in Asian countries. The single Asian study compares to 19 studies fulfilling our inclusion criteria and having been conducted in countries outside of Asia (Abdel Rasoul et al., 2008; Bazylewicz-Walczak et al., 1999; Cole et al., 1997; Daniell et al., 1992; Delgado et al., 2004; Durham et al., 1965; Eckerman et al., 2007; Farahat et al., 2003; Fiedler et al., 1997; Kamel et al., 2003; Korsak and Sato, 1977; Mackenzie Ross et al., 2010; Maizlish et al., 1987; Rodnitzky, 1975; Rohlman et al., 2001; Roldan-Tapia et al., 2006; Rosenstock et al., 1991; Rothlein et al., 2006; Stephens et al., 1996). Due to the fact that occupational and environmental exposure often overlap, we also conducted the literature search without the term "occupational", but this did not alter the outcomes for the Asian countries. It might be argued that Asian studies on pesticides were conducted and published in Asian journals which we could not analyze due to language restrictions. At the current stage we cannot entirely rule out this possibility, but then it still has to be explained why Asia provides 5% of the studies for a meta-analysis on pesticides, but provides 20% of the studies for a meta-analysis on solvents (Meyer-Baron et al., 2008). Both studies made use of the same English language databases for their reviews of the literature. We find a shortage of investigations on the neurobehavioral impact of pesticides also in other parts of the world and many questions, especially on the effects from long-term low-level exposure, remain unanswered. However, the lack of publications on pesticides is particularly marked in Asian countries.

In the more industrialized countries small scale farming and self-employment may be reasons why pesticides are not considered as a focus of occupational health. In less industrialized countries we encounter small-scale farming and self-employment as well, but in addition the reasons outlined by London (2009), namely poor case detection, lack of skilled personnel, facilities and equipment, inadequate information systems, and significant competing causes of ill-health may contribute to the lack of studies.

Should it be the case that the finding of an absence of Asian studies be the result of studies being published only in the local language, it could be addressed by setting up databases that include English abstracts for papers whose main text is written in the local language; an example is http://www.koreamed.org/SearchBasic.php.

We could ascertain some Asian studies that investigated or included symptom reports and tentatively it can be concluded that also an exposure-effect relationship was suggested. Those studies with the greatest share of poisonings obtained the most serious symptoms; the exposure was excessive for these participants. The share of participants complaining about symptoms was smaller in those studies where feasibly milder or no cases of poisoning were included. These persons also suffered both from current and long-term exposure, but obviously from a distinctly lower exposure than the first group. The third group seemed to have the lowest exposure-level, but there was a chronic exposure though. However, no final conclusions about the contributions of intensity or duration of exposure to the development of symptoms are possible from the data at hand.

Nevertheless, when symptoms occur and some of them were serious neurological symptoms, it is too late for preventive actions. A precautionary system requires the detection of the earliest signs of the health impact. These subclinical signs, namely the functional deficits caused by neurotoxicants, can be measured by neuropsychological tests. The knowledge about these deficits allows the intervention at an early stage to protect the workers' health from a more detrimental impact of neurotoxic substances. The apparent absence of studies on neurobehavioral effects of pesticides indicates a lost opportunity for prevention in Asia.

4. Solvent neurotoxicity among working children

Significant neuro-anatomical and neuro-maturation changes take place during adolescence and are reflected in maturation of abstract reasoning, affect, and cognition (Andersen, 2003; Brown et al., 2000). Hence, neurotoxic exposures in millions of children <18 years who work in hazardous occupations in developing countries raise concern that those exposures might affect their cognitive and behavioral development. However, few studies have addressed this issue. In Lebanon (population 4.0 million), where recent reports estimate that 100,000 children work, we have documented that male working children 10–17 years old exposed to solvents in a variety of workshops performed much worse on neurobehavioral measures than working children who are not exposed to solvents or non-working schoolchildren (Saddik et al., 2003; Saddik et al., 2005).

The current study compares the neurobehavioral performance of male working children exposed to solvents in mechanics workshops to that of working children who are not exposed to solvents. Because the analysis is still in progress, this paper describes the methods and preliminary descriptive findings on the study participants. The study is a collaborative effort between the American University of Beirut (AUB) in Lebanon and the Oregon Health & Science University (OHSU) in the US.

4.1. Methods

4.1.1. Recruitment of working children—The children were recruited from the neighborhood of *Bab el-Tebbaneh* of the city of Tripoli in north Lebanon. This is one of the poorest urban neighborhoods in Lebanon with overpopulation and recurrent political instability and social unrests (CDR (Council for Development and Reconstruction), 2006). The children were recruited by a team of trained field workers from the study community itself.

The neighborhood was surveyed twice during the period of February-March 2009. Employers were approached and asked if they currently employed children younger than 18 years of age with a minimum of one year overall work experience (not necessarily in the same workshop). Information was noted for later recruitment. In the recruitment phase, the field worker filled in the form with the required details including number of working children at the workshop, their ages and the child's contact information if possible. The employer was asked permission to talk to the child. The objectives of the study were explained to the employer and child independently. The parents/guardians of the children were visited at their homes to explain the study objectives as well. The consent of the employer, the parents or guardians, and the children were secured before the children were assessed. The field workers secured the oral consent/assent of the employer, child, and parents first. Later, a senior field coordinator along with the field worker and a community leader would visit the child at home to secure his written approval and that of his parents/guardians. The team was always accompanied by a known person from the community (community leader) who facilitated the interaction with employers and families.

A total of 389 working children were identified from 332 workshops. Recruitment for the pilot testing (July-August 2009) and actual testing (October 2009–May 2010) resulted in the following: 21 for pilot testing; 55 not located; 20 found not eligible; 113 refusals (74 children, 7 employers, 14 parents, 18 no show after consent). A total of 180 working children were enrolled in the study for a response rate of 64% (201 enrolled or piloted/314 located and eligible).

4.1.2. Assessment of recruited children—Children were invited to a local center, managed by a non-governmental organization named Rene Moawad Foundation, for interviewing and assessment. All assessments were performed in isolated rooms to ensure privacy. Upon their arrival at the center, children were assigned to one of three preset sequences of testing.

The children were interviewed using a standardized and piloted questionnaire, examined by a general practitioner, and assessed for neurobehavioral function using Grooved Pegboard, Profile of Mood Scale (POMS), and selected tests on the Behavioral Assessment and Research System (BARS). The children were also tested for contrast sensitivity, color vision, and blood lead level. BARS tests included Tapping Test, Symbol Digit Test, Simple Reaction Time, Digit Span Test, Progressive Ratio Test, Selective Attention Test, Serial Digit Learning Test, Continuous Performance Test, Match-to-Sample Test, and Reversal Learning Test.

Questionnaire: The questionnaire was written in local colloquial language and was administered by trained interviewers. The last section of the questionnaire included a non-verbal analogue (neutral to smiling face) of POMS where the children were asked in response to 8 different stimuli to mark with a pencil where they fell on the scale.

Physical examination: A nurse measured the height, weight, blood pressure, and pulse and respiratory rates of the child, then a general practitioner examined the child and recorded on a standardized form her overall assessment of all systems with a focus on the nervous system, specifically alertness and mental status, gait, motor functions, deep tendon reflexes, cerebellar functions, cranial nerves (II–XII), and sensory system (vibration, joint, and position sense). The physical examination lasted 15–20 minutes.

Grooved Pegboard: The Grooved Pegboard is a manipulative dexterity test. This unit consists of pegs and 25 holes with randomly positioned slots. Pegs, which have a key along one side, must be rotated to match the hole before they can be inserted.

The testing started with the use of the dominant hand. The tester-interviewer encouraged the child to perform the task as quickly as possible, telling him to speed up if necessary. Frequently, it was necessary to point out the first hole of a new row, particularly during the non-dominant hand trial. Only one peg was to be picked up at a time and the child was immediately reminded if more than one was picked up.

Color vision: The Lanthony D-15 desaturated color panel was used to assess color discrimination and dyschromatopsia. The child was asked to arrange a set of 14 caps in the order of increased color grade starting from the reference cap.

The test was first performed with 2 eyes open to familiarize the participants with what is expected of them. Later each eye was tested separately. No time limit was set. After each stage, the child was asked to check again and see if any modifications were needed to ensure that the colors are arranged gradually. Most individuals took approximately 1 minute to complete the test. A Color Confusion Index (CCI) was computed for each eye which is a quantitative score accounting for the color differences between the adjacent caps and the total distance between caps.

Contrast Sensitivity: Contrast Sensitivity was assessed using the Contrast Sensitivity view-in Tester (CST 1800 Digital) FACT chart at 5 frequencies (1.5, 3, 6, 12, and 18 cycles per degree), on illumination photopic 85cd/m^2, with no glare. The mean threshold values for each and both eyes were computed using software provided by the manufacturer. Eyes were tested, both open then left or right closed, consecutively with a few seconds break between each test to relax the eye.

Grade level placement: Children were screened for literacy and assigned a grade-level proficiency in reading skills. Since there is no such national screening test, we adopted the Rene Moawad Foundation (RMF) grade level test. RMF uses this questionnaire to evaluate the literacy level of school drop-outs before enrolling in their literacy program.

BARS: The computer-based Behavioral Assessment and Research System (BARS) has been developed in the OHSU laboratory of Dr. Kent Anger and Dr. Diane Rohlman to assess neurobehavioral functioning (Rohlman et al., 2003).

Four BARS units supplied with headphones were placed two in a room with tested children seated in opposite directions. No conversation was permitted between the children during testing.

At the beginning of the session, the examiner-tester explained to the child that headphones should be properly worn at all times, and that he should pay attention to the oral instructions given by the computer, apply whatever is requested by the instructions, and only use the 9 button placed in front of them to respond. The children were also informed that the test might take some time and they were encouraged to finish it all.

The examiners/testers observed the children during the test and registered any behavioral reactions, questions asked, or if assistance was requested. They also kept track of the progress of the tests in case of computer freezes and registered general remarks regarding the process such as freezing of tests, recoding of new ID etc.

The team faced some technical problems with the BARS mostly related to the frequent electricity cutoffs in the neighborhood. In addition, the BARS test instructions were written in Arabic but spoken in Egyptian accent. Some children had difficulty reading or even understanding the instructions which necessitated the help and intervention of the trainers. Current efforts are underway to develop a new BARS PC-version with instructions read in the local Lebanese dialect, using functional rather than word-for-word translation, accounting for the expected literacy of the study population.

Blood lead level: The effect of exposure to solvents on neurobehavioral performance will be statistically adjusted for exposure to lead, measured by blood lead level. The blood lead level was measured at the end of the session using a portable anodic stripping voltmeter (LeadCare®). This method strongly correlates with laboratory-based graphite furnace atomic absorption spectrophotometry (GFAAS) and is recommended for pediatric and working populations (Pineau et al., 2002; Rubin et al., 2002; Taylor et al., 2001). The nurse explained to the child the procedure of testing for blood lead level and after securing child's agreement the nurse followed the procedure as prescribed by the manufacturer. The results were reported in three minutes.

4.2. Findings

A total of 180 working children (≤ 18 years) were recruited into the study. Of these, 90 (50%) worked in car repair shops with potential exposure to benzene and other solvents and another 90 (50%) children worked in different shops (e.g., bakeries) with no exposure to solvents. Children working in "wet occupations" (e.g., car wash, chicken abattoir) or jobs with exposure to dust or furniture spray painting were excluded. Following is a brief description of the 180 recruited children (exposed and non-exposed to solvents).

More than one third of the working children (35.6%) were 14 years or younger, with 41.7% between 15–16 years. A total of 125 (71%) left school at grade 5 or before and 139 (78.5%) attended public schools. They started working full time at a mean age of 12.80 year (SD 1.93) with 41 (22.8%) starting between 7–11 years of age.

The majority lived with both parents (85.6%), had parents with low education (41.7% of mothers and 37.8% of fathers are illiterate), and worked with employers not related to their families (60.6%). The mean hours of work a day was 9.6 (SD 1.79), with 103 (57.9%) reporting only one break during the working day. A total of 25 (13.9%) were current smokers and 76 (61.7%) reported exposure to solvents at work.

It is worth noting that the research team was warned to expect a high level of delinquency and aggression from the children working in this "violent" neighborhood. Contrary to these perceptions the children were overwhelmingly kind and respectful of time and to people. They were especially kind when listened to talking about their views on issues, lives, and future plans. Some wished they were given a new opportunity to continue their education but in a respectful school environment. Aggressiveness and carrying knives were acknowledged by some and reported as an act of self defense against peers and the dangers of the neighborhood.

5. Neurotoxicity of 1-bromopropane, an alternative to ozone-depleting solvents

When chemicals are suspected to exert a negative impact on human health or the environment, the search for alternatives becomes important. 2-Bromorpopane was one of such alternatives. In the middle of the 1990s, it was introduced into workplaces in developed countries to replace chlorofluorocarbons or 1,1,1-trichloroethane which had been banned because of international agreements for the preservation of the ozone-layer. Subsequently however, it was shown that2-bromopropane cause reproductive and hematopoietic disorders (Kim et al., 1996). Along with the uncovering of its toxicity, 1-bromopropane has been introduced into workplaces as another alternative to ozone-depleting solvents. But, also this substitute had a negative impact; neurologic functions were affected by 1-bromopropane. We sum up here how toxicities of 2-bromopropane and 1-bromopropane have been clarified by animal and human studies in the historical context. We link regulatory changes in Japan to the emerging scientific evidence on the toxicity of both bromopropanes.

5.1. Methods

We reviewed published literature on reproductive, hematopoietic and neurotoxic effects of 2-bromopropane and 1-bromopropane. Both human and animal studies were considered.

5.2. Results

In 1996 a Korean study showed that 2-bromorpopane was associated with reproductive and hematopoietic disorders in female and male workers in Korea (Kim et al., 1996). Among 25 female workers and 8 male workers who had used 2-bromopropane in their workplace, 16 females showed secondary amenorrhea and 6 males showed azoospermia, oligospermia or reduced sperm. Their bone marrows were also affected. The workers had been exposed to 97.4% purity of 2-bromopropane.

To clarify the causative agent for the reproductive and hematopoietic disorders in the workers, we and Korean researchers conducted animal studies with inhalation and intraperitoneal injection of 2-bromopropane (Ichihara et al., 1997b, 1996; Kamijima et al., 1997; Lim et al., 1997; Yu et al., 1997; Yu et al., 1999b). The 9 week-inhalation study showed severe atrophy of testis and reduction of epididymal sperm (Ichihara et al., 1997b, 1996). Our studies also showed that also exposure to 2-bromopropane decreased the number of spermatogenic cells and, at higher concentrations, induced the Sertoli-only syndrome (Ichihara et al. 1996, 1997b). Subsequent studies in female rats showed that 2-bromopropane exposure induced reduction of primordial follicles, which was accompanied by apoptosis of oocytes (Yu et al. 1999b). The serial observations of another study showed that exposure to 2-bromopropane targeted spermatogonia after subcutaneous injection to male rats (Omura et al., 1999).

Thus, the animal studies revealed that 2-bromopropane was the causative agent for reproductive and hematopoietic disorders of the Korean workers. The Japan Ministry of Labor at that time warned the companies against the risk of using 2-bromopropane as a cleaning solvent. Instead of 2-bromopropane, the isomer 1-bromopropane was newly introduced into workplaces. Beside the reproductive and hematopoietic effects also the lower mutagenicity of 1-brompropane compared to 2-bromopropane contributed to this decision (Kim et al., 1998; Maeng and Yu, 1997).

However, in a comparative study of 2-bromopropane and 1-bromopropane in rats, a greater neurotoxic potential was shown for 1-bromopropane (Yu et al. 1998; Yu et al., 2001a). The animal experiments (Ichihara et al., 2000a; Ichihara et al., 1998; Yu et al., 1998; Yu et al., 2001b) revealed that exposure to 1-bromopropane induced degeneration of the myelin sheath in the peripheral nerve as well as swelling of preterminal axons in gracile nucleus of medulla oblongata in rats (Ichihara et al., 2000a; Ichihara et al., 1998; Yu et al., 1998). The study by Ichihara et al. (2000a) showed weakness in grip strength of limbs and slowed motor nerve conduction velocity as well as an elongated distal latency in tail nerve. The inhalation study by Ichihara et al. (2000b) showed that 1-bromopropane did not reduce the number of spermatogenic cells in the testis but inhibited spermiation from the seminiferous tubles in the testis, which is considered to be mediated by Sertoli cell dysfunction. The inhalation study of 1-bromopropane in female rats (Yamada et al., 2003) showed that 1-bromopropane mainly inhibited development of follicles in ovary but did not diminish the number of primordial follicles, different from 2-bromopropane-that induced adverse effects on female reproductive organs. Table 2 gives an overview on the effects of 2-bromopropane and 1-bromopropane.

Subsequently, a dozen of human cases showing neurologic disorders induced by 1-bromopropane exposure were reported in the United States (CDC, 2008; Ichihara et al., 2002; Majersik et al., 2007; Raymond and Ford, 2007; Sclar, 1999). The human cases showed numbness, paresthesia or hyperreflexia in lower limbs, diminished vibration sense, ataxia or difficulty in walking or standing (Ichihara et al., 2011). The cases also showed memory disturbances and depressive or unstable mood.

In Chinese factories 60 female workers and 26 male workers producing 1-bromopropane were examined as well as age-and sex-matched control workers (Ichihara et al., 2004; Li et al., 2010). The evaluation of the vibration sense and electrophysiological parameters in the lower limbs and the estimates of individual exposure levels using passive samplers showed dose-dependent neurologic abnormalities in the workers.

In summary, findings from human studies suggest that sensory nerves were affected by 1-bromopropane exposure, as shown by loss of vibration sense, anesthesia or dysesthesia mostly in the lower extremities. The cases showed that the muscle atrophy was not prominent, different from hexane intoxications. Ataxia or gait difficulty was observed and some cases showed positive signs in Romberg test, suggesting a contribution of sensory deficits to the ataxia (Ichihara et al., 2011). Many cases showed hyperreflexia suggesting lesions in the central nervous system. The cases also showed mood changes and possible cognitive or memory disturbances.

5.3 Discussion

Of interest is how the above mentioned animal studies explain the signs or symptoms in human cases intoxicated with 1-bromopropane. The animal studies showed degeneration of myelin in the peripheral nerve and degeneration of pre-terminal axons in gracile nucleus in medulla oblongata in rats. These findings may explain the sensory problems in human cases of 1-bromopropane intoxication. On the other hand, there were limited morphological changes induced by 1-bromopropane exposures in the central nervous system of animals (Fueta et al., 2004; Ichihara et al., 2000a). We consider the morphological changes in the central nervous system as a more robust indicator of toxicity than biochemical or physiological parameters, because of the high plasticity of the central nervous system (Ichihara et al. 2011).

In this context a recent study in rats is of importance (Mohideen et al., 2011). It showed a dose-dependent decrease in noradrenergic axons in the prefrontal cortex and amygdalae induced by 1-bromopropane exposure. The study is the first to show clear morphological changes in the cortex region of the brain after exposure to 1-bromopropane. The decrease in noradrenergic axons was remarkable and the results show that the immunohistochemistry is a promising method to identify the morphological changes in the central nervous system induced by environmental neurotoxic chemicals. Further studies are needed to clarify endpoints to explain the neurological signs or symptoms in human cases intoxicated with 1-bromopropane. The study will be also useful to establish an animal model for evaluating the possible central nervous system toxicity of newly-introduced industrial chemicals.

6. Summary

The Asian approaches to neurotoxicological effects on human health are as manifold as the countries belonging to Asia. Nevertheless a few more general thoughts might be derived from the contributions at hand. We live in a globalized world as regards the production and selling of goods, but it is obviously much more difficult to globalize the knowledge about occupational diseases that are related to the different branches of the economy. Apparently it is the personal experience of sometimes serious outbreaks that triggers or contributes to a public interest in questions of occupational diseases, as it was shown by the Korean experiences or by the study on child workers. UNICEF and welfare groups have highlighted the fates of working children and raised public awareness during the last decade. It can be assumed that the demand for a protective and preventive occupational health care is also fostered, when the concerns are picked up by workers' associations. We saw that in a field where workers associations are not common, namely agriculture, problems might go largely unattended. The summary on the Korean development suggested that the public awareness is more important than the mere number of cases of occupational diseases, which was apparently not distinctly different among some diseases. A highly developed industry and its demand for a healthy workforce, but also a regulatory framework that lowers current exposures and allows a shift of the occupational health objectives to a more preventive stage seem to be important driving forces for highly sophisticated research on and prevention of occupational diseases.

Conclusion

Summarizing it can be concluded that public awareness is one important aspect that health effects of neurotoxicants become a matter of research and regulation. In the absence of this awareness risks may go unattended and opportunities for prevention are missed. Still efforts have to be spent in Asia to detect the earliest stages of occupational diseases.

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Table 1

Asian studies on the neurotoxic impact of pesticides

Country and reference	Sample	Severity of exposure	Findings
China (He et al., 1989)	573 patients	100% poisoning (also intentional)	nausea 60% dizziness 61%
Sri Lanka (Smit et al., 2003)	94 farmers	29% poisoning	nausea RR = 2.6 excessive salivation RR = 6.56 dizziness RR = 2.63
Jordan (Saadeh et al., 1996)	70 patients	100% poisoning (also intentional)	nausea/vomiting 73% excessive salivation 73% headache/dizziness 63%
Korea (Hong et al., 2008)	12 patients	suspected poisoning	nausea/vomiting 92% headache 84%
Indonesia (Kishi et al., 1995)	282 farmers	% poisoning unknown	dizziness 21% nausea 11% salivation 13%
Emirates (Almehdi et al., 2000)	87 farmworkers	% poisoning unknown	nausea/vomiting 15% headache 44%
China (Chen et al., 1991)	834 spraymen	poisoning < 1%	dizziness 15% nausea 8%
Israel (Richter et al., 1992)	90 agricultural workers and residents	no acute poisoning	not available
India (Srivastava et al., 2000)	59 workers	asymptomatic	headache 4%

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Table 2

Comparison of the effects of 1-bromopropane and 2-bromopropane in rats

	2-bromopropane		1-bromopropane
Mutagenicity	+ (Maeng and Yu, 1997)	>(Kim et al., 1998)	
Male Reproductive toxicity (target in testis)	+ (Ichihara et al., 1997b, 1996; Omura et al., 1999) (Spermatogonia		+ (Ichihara et al., 2000b) (Spermiation, Sertoli (Ichihara et al., 2000b)
Hematopoietic toxicity	+ (Ichihara et al., 1997a; Nakajima T, 1997)	> (Ichihara et al., 2000b)	
Neurotoxicity	+(Yu et al., 1999a; Yu et al., 2001b)	<(Yu et al., 2001b)	+++ (Ichihara et al., 2000a; Ichihara et al., 1998; Yu et al., 1998; Yu et al., 2001b)