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Chulabhorn Research Institute

INTERNATIONAL CENTRE FOR ENVIRONMENTAL AND INDUSTRIAL TOXICOLOGY (ICEIT)

CRI's ICEIT has been designated as a
"UNEP Centre of Excellence for Environmental and Industrial Toxicology".

Toxicology of Pesticides and Industrial Chemicals: Occupational Health and Safety

The above topic was the subject of two training courses organized by the Chulabhorn Research Institute in February 2003. The first three day course was held in Bangkok, 18–22 February and the second in Hanoi, 24-28 February. HRH Princess Chulabhorn presided over the opening of both training courses.

The Bangkok training course took place at CRI and was attended by 30 participants from 10 countries. It was part of CRI's ongoing program in human resource development for countries in the developing world, particularly countries in the Asia Pacific region.

The Hanoi course was designed specifically for Vietnamese officials, from govern-

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Toxicology of Pesticides and Industrial Chemicals: Occupational Health and Safety

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ment and academia, as well as the private sector. This further demonstrates the close links between the Chulabhorn Research Institute and the Department of Science, Technology and Environment in Hanoi, a partnership that receives the support of Thailand's Department of Economic and Technical Cooperation.

At the opening ceremony in both Bangkok and Hanoi, HRH Princess Chulabhorn delivered a keynote lecture on Industrial Chemicals and Pesticides: International and National Concerns on their Adverse Effects.

The topics covered at each training course were: Toxicity testing; Respiratory system toxicology; Skin toxicology; Neurotoxicology; Hepatotoxicity; Pesticide use and toxicology; Hazardous waste; Occupational carcinogenesis; Industrial chemical toxicology; Environmental distribution of chemicals; Principles of ecotoxicology-data interpretation and risk assessment; Human biomonitoring; and Occupational exposure standards and guidelines.

New research on the endocrine-disrupting effects of pesticides

There is growing concern in the scientific community regarding the effects of xenobiotic chemicals on the endocrine regulation of reproduction, growth and development of wildlife and the subsequent impact on human life.

A central focus of research is to identify environmental contaminants with potential endocrine-disrupting effects in order to gain a fuller understanding of the impact these chemicals have on ecosystems and on the multigenerational physiology of organisms within those ecosystems.

Freshwater fish are particularly suitable sentinels for environmental xenobiotics due to the osmotic imbalance that exists between their aquatic environment and their body fluids, which results in a very intimate relationship between these animals and their environments. Freshwater teleosts of the genus *Xiphophorus* have long served as excellent research models for the study of the relationships and interactions of the genome, environment and neuroendocrine system in the regulation of physiological processes, especially reproduction, in vertebrates.

A number of leading research laboratories in the United States have focused research on the study of the neuroendocrine regulation of growth, reproductive function and aging.

This work has, for several decades, made use of the freshwater teleosts of the genus *Xiphophorus,* particularly *X. maculatus,* commonly known as the platyfish, and *X. helleri,* commonly known as the swordtail, as research models. These animals have been the subject of intensive scientific investigation with the result that the genetics and physiological systems of these animals are both well known and well documented. In more recent years, methods by which the accumulated knowledge of the *Xiphophorus* model could be utilized to assess the effects of endocrine-disrupting compounds (EDCs) on vertebrate physiology have been detailed and now a recently published report describes ongoing investigations involving two purported EDCs, methoxychlor and nonylphenol.

Methoxychlor is a pesticide that was developed to replace DDT. It is approved for use on animals, crops and in animal feed. It has also been extensively used in Canada for the control of biting flies and is effective against mosquitoes. Although it is widely believed that methoxychlor possesses estrogenic activity, it is significantly less persistent in the environment than its more notorious predecessor, DDT.

Nonylphenol is an alkylphenol polyethoxylate (APE) that is discharged into the aquatic environment during paper and pulp production, textile manufacturing, plastic and petroleum processing and in usage of household and industrial cleaning products. In addition, nonylphenol and related substances are known to leach out of plastics and polystyrene in quantities that, although minute, are sufficient to have an estrogenic effect on living cells.

A comparison of the results of the two studies confirms that both nonylphenol and methoxychlor can have significant adverse effects on vertebrate physiology even at concentrations that have been deemed "acceptable". This would clearly demand a reexamination of the methods by which environmental standards are developed, and of the standards themselves.

Source: Neurotoxicology and Teratology, No. 24, 2002.

THE ETHICS OF HUMAN PESTICIDE EXPERIMENTS

Experiments on human volunteers to see how much of a pesticide is needed to trigger a metabolic response is often claimed to be the best safety data. Yet despite their utility, such tests create a dilemma for the U.S. Environmental Protection Agency (EPA). If it accepts these data in its safety review, the agency may well be accused of condoning what many would consider unethical practices.

In late 2001, the agency turned to the National Academy of Sciences (NAS) for advice. The new NAS panel has now heard from both advocates and opponents of dosing experiments. Their vehement debate underlines the difficulty the panel faces in trying to untangle the scientific and ethical questions.

The panel's recommendation, due in December, could be far reaching. In addition to pesticides, EPA has recently received data on humans deliberately exposed to groundwater contaminants, and the agency hopes to continue to use outside human studies testing the toxicity of air pollutants.

The trigger for this recent spate of testing was the 1996 Food Quality Protection Act which mandated that EPA reduce acceptable levels of pesticides in foods to protect children. Up to that point, EPA had set a limit several orders of magnitude smaller than the minimum dose that causes effects in animals. Faced with the new law, pesticide companies began supplementing animal studies with human data in an effort to avoid a 10-fold safety factor built in to account for possible higher sensitivity in people; this could offset the tighter limits for children. Since the new law was enacted, companies have submitted about two dozen human toxicity studies to EPA.

In 1998, the Environmental Working Group (EWG) in Washington, D.C., questioned the ethics of these studies, in which volunteers (mostly in the United Kingdom) were paid $600 or more. EPA officials had become concerned as well and had shelved the studies until an advisory committee gave its view. That committee issued a report in 2000 saying that some human tests, such as metabolism studies, were acceptable under strict conditions—but most dosing experiments were not.

Many argue that pesticide-dosing tests are indeed unethical because they are carried out expressly for the benefit of industry and offer no conceivable advantage to society. However, some toxicologists have suggested that if tests were well designed ethically and scientifically, there were ways in which the public might benefit from the data.

The major problem with all human data used by EPA is that, unlike the Food and Drug Administration, it has no protocols for human studies and lacks a stringent policy for ethics reviews of human data. There is an urgent need for well defined, enforceable standards.

Source: Science, Vol. 299, No. 5605, January 2003.

THE VULNERABLE PERIOD IN THE DEVELOPMENTAL NEUROTOXICITY OF CHLORPYRIFOS

Chlorpyrifos (CPF) remains a widely used pesticide even though there is considerable concern over the potential consequences of fetal and childhood exposure. The systemic toxicity of CPF primarily reflects cholinergic hyperstimulation as a result of the inhibition of cholinesterase activity, and immature organisms are more susceptible to CPF-induced toxicity than are adults.

However, several recent studies suggest that CPF affects relatively late events in brain development, centered around the proliferation, differentiation, and functioning of glial cells. These are the cells that provide metabolic support for neurons and that guide axons to their proper targets within the developing nervous system.

Such findings raise the issue of identifying the critical time for adverse effects of CPF on neurodevelopment since, if late occurring processes are involved, vulnerability will extend into childhood, a period in which exposures may be particularly high.

Using the rat model, previous studies have found that exposure of neonatal rats to CPF produced brain cell damage and loss, with resultant abnormalities of synaptic development. Recent studies have now used the same biomarkers to examine prenatal CPF treatment in order to define the critical period of vulnerability.

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The Third Meeting of the Network for Scientific Cooperation in Environmental Toxicology, 17 February 2003, Bangkok, Thailand

The members of the network participating in the meeting comprised 9 delegates from 8 countries, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam.

The meeting was attended by 4 representatives of the Chulabhorn Research Institute, 4 international experts, from Canada, UK and USA, as well as 17 observers from 9 countries. In her welcoming address to open the meeting, Dr. *Khunying* Mathuros Ruchirawat, Vice President for Research at CRI, emphasized the importance of the Network for Scientific Cooperation in Environmental Toxicology in its role of monitoring problems arising from the impact of toxic substances on the environment of countries in the Southeast Asian region. Further, the network had an important role in highlighting improved strategies for dealing with environmental problems and sharing this information with member countries, in developing regional resources of networking to improve the exchange of information in such areas as toxicity research and biotechnology, enabling effective solutions and procedures implemented to improve the quality of the environment, thus contributing to the sustainable development of the region.

Professor Nay Htun, Executive Director for Asia and the Pacific, University for Peace, and Professor R.C. Shank, Professor and Chair of the Department of Community and Environmental Medicine, University of California, jointly chaired the meeting.

In the morning session and the first part of the afternoon session, the delegates of the 9 countries represented reported on the status of environmental toxicology, strengths and weaknesses of current approaches in dealing with toxicological impacts and results so far achieved in their respective countries.

The main points of concern raised in the country papers were as follows:

Cambodia The current dependence on the use of pesticides to improve agricultural yield and the concomitant hazards to human health and the environment.

The urgent need to achieve sound environmental management of hazardous waste as part of a national strategy plan to include legislation on the reduction and elimination of hazardous waste generation.

Indonesia The main environmental toxicology problems currently being addressed are water pollution caused by uncontrolled industrial effluents and air pollution from industrial discharge.

The dumping of solid and liquid waste from both industrial and domestic sources are affecting water, land and soil pollution. Moreover, uncontrolled use of pesticides is resulting in toxic substances entering the food chain and causing groundwater pollution.

Lao PDR The government has signed the convention on the persistent organic pollutants (POPs) and is currently implementing the POPs Enabling Activities Project which will focus on the formulation of a National Plan.

Environmental toxicology issues mainly result from intensive agricultural practices. However, the government has adopted a policy of strongly promoting organic farming. Other issues are mainly due to industrial activities, and economic incentives are seen as the way to address problems of environmental toxicology. Many issues are, however, transboundary in nature and need to be addressed conjointly with other countries in the region.

Malaysia The Department of the Environment has provided some guidelines on the characterization of potential hazardous wastes. However, the inability to establish the toxic or non-toxic property of industrial wastes has hindered the development of treatment technologies that could lead to their reuse or recycling.

The Environmental Quality (scheduled wastes) Regulations together with Occupational Safety and Health Regulations have been pivotal in ensuring proper management of hazardous wastes and chemicals. However, solid waste management remains a major problem and leachates from dump sites could contaminate underground water, affecting the future supply of clean potable water.

Myanmar The degree of air and water pollution caused by industry or agriculture has been minimal due to the still low level of industrialization and he relatively small amounts of chemicals used in agriculture.

Future industrial expansion is expected to add to the hazardous industrial wastes currently generated by factories such as paper mills, leather factories, textile factories and the mining industry, with large scale extraction of metals already resulting in hazardous waste problems.

Philippines The country today is faced with the double burden of diseases – communicable and non-communicable diseases brought about by the hazards arising from the interaction of man's activities and the environment. The hazards are caused by industrialization and urbanization, affecting the quality of air and water. However, also of immediate concern are deforestation and concomitant soil degradation as well as hazards arising from the widespread use of chemicals.

Environmental toxicology results not only from large-scale industries but increasingly from small-scale mining practices where often the direct discharge of waste water containing mercury contaminates marine life and enters the food chain. In the soil, concern is not limited to mercury but includes lead, cadmium, and arsenic. The impact on human health is becoming increasingly evident.

Singapore The island-state has had to address environmental issues related to rapid urban growth and industrialization; and because of limited land area, sustainable development has become an obligatory path to follow. However, cross border pollution also affects ecological and environmental conditions and cannot be controlled.

Strict control of toxic and hazardous substances, urban and life style regulation and careful monitoring of sources of possible food contamination can be achieved by proper planning and management, ensuring that economic and industrial growth need not be at the expense of health and the environment. However scarcity of basic resources such as potable water remains a challenge for the future.

Thailand The disposal of both domestic and industrial solid waste is now a major environmental concern. Despite some progress at governmental control levels, widespread contamination exists and in some instances has created major health problems. The dumping of hazardous solid wastes originating from other countries is also a problem. The reality is that the controls of the Basel convention are not imposed and responsibility is not accepted for uncontrolled dumping.

The use of chemicals in agriculture and industry is the main cause of many environmental problems, particularly since there is a tendency to import cheap chemicals from India and Pakistan, which are not identified by the UN code.

Because of the risk of spillage of chemical substances and industrial accidents involving toxic effluents, emergency response plans need to be improved.

To facilitate identification of toxic substances and ensure reliable data, an environmental research laboratory is to be set up by the Department of Environmental Quality Promotion.

Vietnam The use of pesticides in agriculture remains a serious problem with 300 tons of pesticides currently used annually in 61 provinces.

As with other countries in the region, the treatment of hazardous waste is high on the list of government priorities. The effect of Agent Orange is still a contentious issue with residual amounts posing health concerns in parts of the country.

Regional resources for networking

Certain key concepts emerged from the discussions of the country papers suggesting a need in future for the network to focus on specific problems. Two problems in particular were identified as needing regional resources to be channelled into research and development:

1) treatment of hazardous waste
2) greater attention to environmental toxicology problems that are essentially trans boundary in nature.

There was agreement that the three main goals of the network should be further resourced, namely:

1) information exchange
2) capacity building
3) research.

Individual members of the network undertook to serve as focal points for specific areas of concern that they were engaged in or where institutions in their countries were particularly active.

More training seminars were needed to build up the region's capability in environmental toxicology and these seminars could be organized by network members providing in-kind support to attract outside funding.

These possibilities are to be explored and remain a priority area for the network.

In closing the meeting, Professor Shank and Professor Nay Htun restated the great importance of continuing the work of regional collaboration in environmental toxicology through the network. All contributions to the meeting had been, in the view of the two chairpersons, (of an exceptionally high standard) with insightful discussion establishing a useful roadmap for the ongoing activities of the network.

WHO/CRI WORKSHOP ON HEALTHY ENVIRONMENTS FOR CHILDREN
3-5 February 2003, Pattaya, Thailand

HRH Princess Chulabhorn opened this three day meeting, jointly sponsored and organized by the World Health Organization and the Chulabhron Research Institute, on the promotion of collaborative research on solving problems relating to environmental risks to children's health.

This workshop was organized in order to carry forward the work of the international conference that had been hosted earlier by the Chulabhorn Research Institute in March 2003 in Bangkok. That conference had identified areas of concern in the main environmental threats to the health of children in countries throughout the world.

The purpose of the Pattaya workshop was to determine the ways by which research capacity in environmental health and toxicology, and the effects of the specific hazards that threaten children's health, could be developed and improved through an integrated and multisectional approach.

In her opening address at the workshop, HRH Princess Chulabhorn expressed the view that this goal could best be achieved through the development of networks among the countries represented by the participants in the workshop, to explore areas of mutual endeavor and the sharing of resources, since it was through collaborative support and the judicious use of human and material resources that progress in this vitally important area of research could be made.

The workshop was attended by 35 specialist participants invited by WHO and CRI.

Health effects of exposure to potassium chlorate

Potassium chlorate ($KClO_3$) is an oxidizing agent that has been widely used in a variety of applications, e.g., the manufacture of herbicides, matches, paints, cleaning products, and explosives. Since it was inadvertently discovered in 1998 as a substance that would stimulate out-of-season longan blossoming, it has been pervasively used among longan growers, especially in the northern region of Thailand.

However, there are serious health effects resulting from exposure to $KClO_3$ dosage that can be categorized as both acute and chronic.

The acute toxicities include irritation of the respiratory tract (sore throat, coughing, etc.) after inhalation, gastrointestinal upset (nausea, vomiting, diarrhea, abdominal pain, etc.) after ingestion, and redness and pain of the skin after dermal contact. If $KClO_3$ is absorbed into the circulation in high dose, it could cause hemolysis, methemoglobinemia, cyanosis, anuria, convulsion, and coma, These reactions are due to the fact that, when hemoglobin is oxidized to methemoglobin, heme iron becomes Fe^{3+} and is incapable of binding oxygen. It also may damage the liver and kidneys, leading to death due to renal failure. If repeatedly exposed to $KClO_3$ in small amounts (chronic exposure), a person could develop loss of appetite and weight. No evidence of mutagenic effects or tumor promotion, however, has been reported. A recent descriptive study revealed that longan growers who used $KClO_3$ as a stimulant in their orchards showed hematological abnormalities of anemia, leukopenia, thrombocytopenia, and methemoglobinemia, with the mean values (except for mean hemoglobin and mean leukocyte) being statistically different from those of the normal population (p-value<0.0001), suggesting that the longan growers might be at risk of $KClO_3$ toxicities. Since $KClO_3$, when absorbed, could be directly toxic to hemoglobin by oxidizing it to methemoglobin, the study sets out to prove whether $KClO_3$ could induce methemoglobinemia in the longan growers who routinely use $KClO_3$ as a longan stimulant.

The laboratory investigations in the longan growers show the mean $\pm$ SD of pre-and post-$KClO_3$ exposure methemoglogin levels to 1.16 $\pm$ 0.12 and 1.36 $\pm$ 0.13 per cent, which are higher than those of Bangkok residents studied during the period 1995-2000, which were in the range of 0.20 $\pm$ 0.32 to 1.14 $\pm$ 0.99 per cent. In addition, the blood testing results reveal consistently higher levels of methemoglobin after using $KClO_3$ in the longan stimulation process, doubtlessly indicating that $KClO_3$ could induce methemoglobinemia. This is not surprising since $KClO_3$ is a strong oxidizing agent.

The results suggest that longan growers are at risk of developing methemoglobinemia, even if the abnormality is of a mild degree. For the sake of occupational health and safety, the parties concerned should be aware of the dangers and take measures to strengthen health educational campaigns to convince longan growers to realize the importance of adequate personal protection.

Source: Intern Med J Thai, Vol.18, No.1, Jan.-Mar. 2002.

AGRICULTURAL PUMPING LINKED TO ARSENIC POISONING

In Bangladesh, irrigation wells have helped end deadly famines, but at the same time millions of other wells dug to provide safe drinking water have been found to contain arsenic from ancient sediments endangering human health.

Now a recent study suggests that agricultural pumping might be a factor influencing the release of arsenic into drinking water. However, the finding is controversial with some experts cautioning that the finding may not be broadly applicable.

Researchers involved in the study analyzed the groundwater chemistry in the Munshiganj District in southern Bangladesh, where many drinking wells are seriously contaminated.

The researchers drilled 15 new wells and then set out to alter groundwater chemistry as they suspect pumping does. In one case they injected water containing molasses, which is rich in organic carbon; arsenic levels increased substantially within days. The team suspects that the increase occurred because the organic carbon reduced and then dissolved the iron oxides that bear arsenic. In another experiment, injections of nitrate caused arsenic levels in the aquifer to plummet 80%, also within days. Nitrate oxidizes dissolved iron, which then precipitates along with arsenic. The team believes that irrigation pumping might lower or raise arsenic levels by either mechanism, for example, by pulling in oxygenated water from sandy sediments or by drawing down organic carbon-rich water from ponds and channels.

At the study site, the researchers believe that this latter mechanism has spiked the drinking water with arsenic. In the upper part of the aquifer, inorganic carbon and methane—byproducts of carbon-based reactions that liberate arsenic—are roughly 40 years old, about the same age as irrigation pumping.

At the study site acceptable arsenic levels were found at about 160 meters, which suggests that deeper wells could reduce the arsenic problem. Other strategies include developing filtration techniques and trying to persuade villagers to switch to more distant shallow wells that are still safe.

Source: Science, Vol. 298, November 2002.

HEALTH RISKS FROM USE OF PHTHALATES

An expert panel convened by the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) has announced that after intensive evaluation of seven phthalates, only one presents a serious concern to human reproduction or development. Di(2-ethylhexyl) phthalate, or DEHP, is considered of serious concern for the possibility of adverse effects on the developing reproductive tract of male infants exposed to high concentrations of the phthalate through medical procedures using phthalate-containing equipment such as intravenous bags and tubing.

Created in 1998 by the NTP and the NIEHS to assess the human reproductive health risks associated with exposures to environmental chemicals, the CERHR announced in April 1999 that it was turning its attention to the risks posed by seven phthalates, which are used as plasticizers in a spectrum of polyvinyl chloride-based products ranging from flexible tubing to plastic toys. The phthalates selected for evaluation included DEHP, butyl benzyl phthalate (BBP), di-*n*-butyl phthalate (DBP), di-isononyl phthalate (DINP), di-isodecyl phthalate (DIDP) di-*n*-hexyl phthalale (DnHP), and di-*n*-octyl phthalate (DnOP). The chemicals were selected based on their high production volume, the number of people potentially exposed to them, their use in products especially intended for children (such as toys), and evidence of reproductive or developmental toxicity. To evaluate the seven phthalates, the center brought together a panel of 16 experts in toxicology, epidemiology, and other relevant fields from government, research, and academic institutions from across the United States.

Over a period of 15 months, the panel evaluated the published data for each phthalate to determine whether or not it is likely to present a risk to human reproduction or development.

Source: Environmental Health Perspectives, Vol. 109, No. 6, June 2001.

Chulabhorn Research Institute

Activity Year 2003

International Training Course on *Health / Environmental Risk Assessment* November 20 – 29, 2003, Bangkok, Thailand

Course Contents:

The course will cover: Information for environmental health decision making; Toxic effects of chemicals; Toxicity testing; Human data / epidemiology; Dose-response assessment; Ecological risk assessment; Exposure assessment; Risk characterization; Guideline derivation / standard setting; Risk management; Risk reduction; Risk perception; Risk communication; Case studies

Fellowships for travel and accommodation and meals are available for participants from developing countries. Deadline for submission of written application with full CV including job description is **September 30, 2003**.

Applicants should have: (a) a bachelor degree in biological sciences, toxicology, medicine, pharmacolgy or related areas; (b) a very good command of the English language, particularly in writing and listening comprehension

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Benzene in cigarette smoke – its possible role in the rising rates of leukemia in Thailand

A study jointly conducted by medical institutes in the United States and in Thailand presents new findings on selected components of cigarette smoke (including benzene and 1,3-butadiene) from major brands of cigarettes sold in Thailand.

Cigarette smoke contains more than 4,000 compounds, including such carcinogens as benzene and related compounds (1,3-butadiene, isoprene, toluene and acrolein) associated with hematopoietic and/or lymphatic cancers in studies of mice and/or rats. In humans, epidemiological studies have linked exposure to benzene and butadiene to leukemia. An estimated 8 – 58% of smoking-related leukemia may be due to benzene exposure. Trends in smoking-related cancers in developing countries are of special interest because of the rise in smoking in recent decades and the marketing of cigarettes in Asia by American tobacco companies. This study examined trends in leukemia mortality rates in Thailand, and in the relative frequency of leukemia among incident cancers diagnosed at a large hospital in Bangkok.

The cigarettes tested were filter and non-filter, and with high and "low" tar and nicotine levels. The observed range for benzene, toluene and 1,3-butadiene were found in the range of 25.5 – 63.7, 36.4 – 79.8 and 44.6 – 78.7 µg/cigarette, respectively. The amount of acrolein ranged from 79.9 – 181 µg/cigarette and for isoprene from 313 – 694 µg/cigarette. Yields of these substances showed no correlation with tar deliveries in mainstream smoke. Consumption of tobacco products has increased in Thailand since 1970. This study also showed increases in leukemia mortality rates in Thailand, and in the relative frequency of leukemia among incident cancers diagnosed at a large hospital in Bangkok. Exposure to benzene and related compounds in cigarette smoke may have contributed to these trends. Analytic epidemiological studies are needed on the relationship between these compounds in smoke from tobacco products used in Thailand. These preliminary findings support the need for voluntary and/or government-regulated reduction in smoke yields of benzene and related compounds in tobacco products, and for expanded smoking prevention and cessation efforts in Thailand.

Source: Oncology Reports, Vol. 9, No. 6, November-December 2002.

THE VULNERABLE PERIOD IN THE DEVELOPMENTAL NEUROTOXICITY OF CHLORPYRIFOS

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One group of pregnant rats received CPF on gestational days (GD) 17-20, a peak period of neurogenesis; a second group was treated on GD9-12, the period of neural tube formation. In the GD17-20 group, the threshold for a reduction in maternal weight gain was 5 mg/kg/day; at or below that dose, there was no evidence (GD21) of general fetotoxicity as assessed by the number of fetuses or fetal body and tissue weights. Above the threshold, there was brain sparing (reduced body weight with an increase in brain/body weight ratio) and a targeting of the liver (reduced liver/body weight). Indices of cell packing density (DNA per gram of tissue) and cell number (DNA content) similarly showed effects only on the liver; however, there were significant changes in the protein/DNA ratio, an index of cell size, in fetal brain regions at doses as low as 1 mg/kg, below the threshold for inhibition of fetal brain cholinesterase (2 mg/kg). Indices of cholinergic synaptic development showed significant CPF-induced defects but only at doses above the threshold for cholinesterase inhibition. With earlier CPF treatment (GD9-12), there was no evidence of general fetotoxicity or alterations of brain cell development at doses up to the threshold for maternal toxicity (5 mg/kg), assessed on GD17 and GD21; however, augmentation of cholinergic synaptic markers was detected at doses as low as 1 mg/kg. Compared with previous work on postnatal CPF exposure, the effects seen here required doses closer to the threshold for fetal weight loss; this implies a lower vulnerability in the fetal compared with the neonatal brain. Although delayed neurotoxic effects of prenatal CPF may emerge subsequently in development, these results are consistent with the preferential targeting of late development events such as gliogenesis, axonogenesis, and synaptogenesis.

Source: Environmental Health Perspectives, Vol. 110, No. 11, November 2002.

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