UNITED NATIONS

RC

UNEP/FAO/RC/CRC.2/16/Add.2

United Nations Environment Programme

Food and Agriculture Organization of the United Nations

Distr.: General
1 December 2005

English only

Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade
Chemical Review Committee
Second meeting
Geneva, 13–17 February 2006
Item 5 (b) of the provisional agenda*

Inclusion of chemicals in Annex III of the Rotterdam Convention: review of notifications of final regulatory actions to ban or severely restrict a chemical: mirex

Mirex: supporting documentation provided by Japan

Note by the secretariat

The annex to the present note contains the supporting documentation provided by Japan in support of its final regulatory action on mirex.

* UNEP/FAO/RC/CRC.2/1.

K0584433 131205

Annex

List of supporting documentation on mirex from Japan

The Japanese DNA for the PIC Convention would like to submit the following information on our notification of final regulatory action on Mirex.

I. Supporting Documentation

1. Risk or hazard evaluation referenced in Section 2.3 of the notification form
   See Annex 1

2. Relevant documentation for Section 2.4.1, referring to protecting human health
   As a result of the test conducted under the Law Concerning the Evaluation of Chemical Substances and Regulation of their Manufacture, etc. (abbrev. the Chemical Substances Control Law), it was found that Mirex is persistent, highly bio-accumulative and toxic for a long time, and may cause irreversible environmental pollution and have adverse effects on human health and environment.

3. Any other information used in making the decision to ban this chemical
   No information.

II. Trade Information

1. Manufacture within Japan and the export destination if manufactured
   No manufacture within Japan was reported, hence there is supposed to be no export experience.

2. The date the chemicals were last imported into Japan
   No import experience has been reported.

Focused Summary

1. Introduction

a) The events that led to the regulatory action
   The government of Japan anticipates that persistent and highly bio-accumulative chemical substances with long-term toxicity (e.g. PCBs) may cause irreversible environmental pollution and have adverse effects on human health or the environment.
   In order to prevent environmental pollution, the Chemical Substances Control Law stipulates that hazardous properties of chemicals should be checked based on the existing knowledge or by the tests which are consistent with the methods of the OECD Test Guidelines, conducted by the OECD GLP facilities.
   If persistent and highly bio-accumulative properties with long-term toxicity are detected from chemical substances, they are classified as Class I Specified Chemical Substances and are subject to final regulatory action (ban on manufacture, import, and use).
   As in the case of PCBs which mentioned above, Mirex is included in an annex of the Stockholm Convention on persistent organic pollutants (POPs). The government of Japan, as a Party of the Convention, placed Mirex in the category of Class I Specified Chemical Substances based on the following judgment so that we could implement appropriate measures for the Convention.

1. Based on the report that biodegradation by microorganisms does not take place except, occasionally, under anaerobic conditions and that no direct evidence of degradation was

obtained after 56 days of incubation in freshwater sediments below aerobic or anaerobic conditions, Mirex is considered to be very persistent.

2. Based on the report that BCF for Pimephales promelas after 56 days of exposure is about 51,000, Mirex is considered to be very bio-accumulative.
3. Based on the report that adverse effects especially to the liver is observed under a number of repeat dose toxicity tests for more than 8 months using rats or mice at low dose levels, and that explicit carcinogenicity especially targeting liver, is observed for test animals, Mirex is considered to have a long-term toxicity.

b) Significance of regulatory action, eg one use or many uses, level or degree of exposure
Since 2002, manufacture, import and use of Mirex have been banned, and import of an insecticide for wood which contains Mirex has been banned.

c) An overview of the regulatory system of the notifying country if relevant
The Ministry of Health, Labour and Welfare, the Ministry of Economy, Trade and Industry and the Ministry of the Environment are responsible for the regulation of chemical substances which are persistent, highly bio-accumulative and toxic for a long time. Once a chemical is classified as Class 1 Specified Chemical Substances, manufacture, import, and use of the chemical are practically banned.

The Ministry of Agriculture, Forestry and Fisheries is responsible for the regulation of pesticide for agricultural use on manufacture, distribution, import and use in Japan. Under the Agricultural Chemicals Regulation Law, the manufacture, distribution, import and use of the pesticide is banned without the registration by the Minister of Agriculture, Forestry and Fisheries.
The registration has been conducted with the standards for the toxicity and the residue in water, soil and crops.

d) Scope of the regulatory action – precise description of the chemicals subject to the regulatory action
Aforementioned in b), it has been banned that manufacture, import and use of Mirex and that import an insecticide for wood containing it.

2. Risk Evaluation

a) Key findings of the national risk evaluation
See Annex.

b) Key data reviews consulted and a brief description
See Annex.

c) Reference to national studies, eg toxicological and ecotoxicity studies
See Annex.

d) Summary of actual (potential) human exposure and/or environmental fate
Mirex is detected in Japan, as is shown in Annex.

3. Risk Reduction and Relevance to Other States

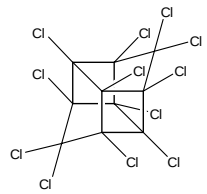
a) Estimates of the quantity of chemicals used, or imported/exported at the time of the regulatory action and if possible information on ongoing trade
No use, export and import of Mirex.

b) Relevance to other States i.e. those with similar conditions of use
No information.

c) Comments on the typical use of the chemical within the notifying country, with comments on possible misuse (if appropriate)
No information.

Annex

<table>
<tr><td>CAS-No.</td><td colspan="2">2385-85-5</td></tr>
<tr><td>Name

Formula</td><td colspan="2">1,1a,2,2,3,3a,4,5,5a,5b,6-dodecachloroacta-hydro-1,3,4-metheno-1H-cyclobuta[cd]pentalene (common name : Mirex)
  $C_{10}Cl_{12}$</td></tr>
<tr><td>Description</td><td colspan="2">White crystalline [1), 2), 3), 4), 5), 6), 7)]</td></tr>
<tr><td>Melting point</td><td colspan="2">485 degrees C [1), 2), 3), 4), 5), 6), 7)]</td></tr>
<tr><td>Boiling point</td><td colspan="2">none (Decomposition begins at 525 degrees C) [1), 2), 3), 4), 5), 6), 7)]</td></tr>
<tr><td>Vapor pressure</td><td colspan="2">3×10^{-7}mmHg(25 degrees C), 6×10^{-6}mmHg(50 degrees C) [1), 2), 3)]</td></tr>
<tr><td>Solubility</td><td colspan="2">Water : below 1 ppb, Tetrahydrofuran : 30%, Carbon disulfide : 18%,
Chloroform : 17%, Dioxane : 15.3%, Xylene : 14.3%,
Benzene : 12.2%, Carbon tetrachloride : 7.2%,
Methyl ethyl ketone : 5.6% [1), 2), 3), 4), 5), 6)]</td></tr>
<tr><td>Persistence</td><td colspan="2">Biodegradation by microorganisms does not take place except, occasionally, under anaerobic conditions. [1)]
No direct evidence of degradation was obtained after 56 days of incubation in freshwater sediments below aerobic or anaerobic conditions [8)]
very persistent</td></tr>
<tr><td>Bio-accumulation</td><td colspan="2">
<table>
<tr><th></th><th>Species</th><th>age</th><th>Exposure period</th><th>BCF</th></tr>
<tr><td>fish</td><td>Lepomis macrochirus
(Bluegill)</td><td></td><td>28 days</td><td>12,274 [8)]</td></tr>
<tr><td></td><td>Pimephales promelas
(Fathead minnow)</td><td></td><td>56 days</td><td>51,400 [1)]</td></tr>
<tr><td>Crustacea</td><td>Hyalla azteca
(Amphipod)</td><td></td><td>28 days</td><td>2,530 [1)]</td></tr>
<tr><td></td><td>Penaeus duorarum
(Pink shrimp)</td><td>larva</td><td>3 weeks</td><td>2,600 [1)]</td></tr>
<tr><td></td><td>Callinectes sapidus
(Blue crab)</td><td>5-day larva
15-day larva
megalopa</td><td>3 weeks
3 weeks
3 weeks</td><td>1,100 [1)]
3,000 [1)]
2,000 [1)]</td></tr>
</table>
very bio-accumulative</td></tr>
<tr><td rowspan="3">Mutagenicity</td><td>Ames</td><td>negative [1)]</td></tr>
<tr><td>chromosomal aberration</td><td>negative [7)]</td></tr>
<tr><td>in vivo dominant lethal test</td><td>negative [1)]</td></tr>
<tr><td rowspan="3">90 days repeat dose toxicity</td><td>Species</td><td>Rat</td></tr>
<tr><td>Vehicle</td><td>Diet</td></tr>
<tr><td>Dose</td><td>5, 20, 80, 320, 1280 ppm
equivalent to 0.25, 1, 4, 16, 64 mg/kg/day</td></tr>
</table>

	NOAEL	20ppm equivalent to 1 mg/kg/day [7)]
	Effects	Vacuolation and swelling at liver cells and increased relative liver weight were observed at 80ppm. Mortality was observed at higher dose.
166 days repeat dose toxicity	Species	Rat
	Vehicle	Diet
	Dose	1, 5, 25 ppm equivalent to 0.05, 0.25, 1.25 mg/kg/day
	NOAEL	below 1ppm equivalent to 0.05 mg/kg/day [7)]
	Effects	Slight hepato-cellular hypertrophy was observed in males at 1ppm and females at 5ppm. Increased relative liver weight was observed at 25ppm.
8 or 12 months repeat dose toxicity	Species	Rat
	Vehicle	Diet
	Dose	5, 30 ppm equivalent to 0.25, 1.5 mg/kg/day
	NOAEL	below 5ppm equivalent to 0.25mg/kg/day [7)]
	Effects	Minimal proliferation of smooth endoplasmic reticulum was observed at 5ppm.
18 months repeat dose toxicity	Species	Mouse
	Vehicle	Diet
	Dose	1, 5, 15, 30 ppm equivalent to 0.05, 0.25, 0.75, 1.5mg/kg/day
	NOAEL	below 1ppm equivalent to 0.05mg/kg/day [7)]
	Effects	Minimal hepatic centrilobular hypertrophy was observed at 1ppm.
13 months repeat dose toxicity	Species	Dog
	Vehicle	Diet
	Dose	4, 20, 100ppm
	NOAEL	20ppm [7)]
	Effects	Mortality, reduced weight gain, increased relative liver weights and decreased relative spleen weights were observed at 100ppm(equivalent to 2.1mg/kg/day).
Reproductive and developmental toxicity	Cessation in reproduction was observed in mice fed 17.8 mg/kg diet for 3 months, and decreased reproduction was observed in the group fed 1.8mg/kg diet. [1)] Reduced weight of offspring and reduced number born alive were observed in mice fed 7.5 mg/kg/day by gavage on gestation days 8-14. [7)] Reduced fatal survival and fatal weight were observed in rat fed 12.5 mg/kg/day in corn oil by gavage on gestation days 6-15. [7)] Edema, tachycardia, heart blocks, and arrhythmias in fetuses were observed in rat fed 5, 6, 7, 20 mg/kg/day in peanut oil by gavage on gestation days 8-15. [7)] Cardiac dysrhythmias, increased perinatal death rate were observed in rat fed 0.25, 0.5 mg/kg/day in oil by gavage on gestation days 15-21. [7)]	

Carcinogenicity	When rats were fed 0.007, 0.07-0.08, 0.7, 1.8-2.0, 3.8-3.9 mg/kg/day dietary concentration : 0.1, 1.0, 10, 25, 50 ppm diet for 104 weeks, liver neoplastic nodule and hepatocellular carcinoma were observed in both male and female rats, and adrenal pheochromocytoma and malignant pheochromocytoma were observed in male rats, and leukemia was observed in female rats. [7), 11)] neoplastic nodule, hepatocellular carcinoma and leukemia were observed in female rats fed 50, 100 ppm diet for 104 weeks. [7), 11)] nternational Agency for Research on Cancer (IARC) classified Mirex as a Group 2B carcinogen, (i.e., possibly carcinogenic to humans).
Kinetics and metabolism	Mirex is stored in adipose tissue to a greater extent than in any other tissue, followed by adrenal gland, peripheral nerve, thyroid gland and skin. It tend to attach itself to muscle and liver partly, and it does not appear to be metabolized in liver. [1), 5)] Its elimination from the body is slow, and its half-life in the body is several months. It is transferred across the placenta to the fetus and is excreted with the milk. [1)]
Effects on man	Acute effect : nausea, vomiting, gut mucosa irritation (diarrhea etc.), fatigue, headache, tremor through central nervous excitement, convulsion, weakness in the legs, etc. respiratory depression through central nervous depression[1), 2), 5), 7)] No reports on occupational exposure and occupational health effects are available. [1), 2), 5), 7)]

Effects on organisms in the environment	fish	*Gambusia affinis* (Western mosquitofish)	96hLC_{50}= 20 mg/l [10)]
		Rainbow trout	96hLC_{50}= 100 mg/l [10)]
	Crustacea	Daphnidae	48hEC_{50}= 0.1 1.0mg/l [10)]
		Procambarus hayi (Crayfish, juvenile)	48hLC_{65}= 1.0×10^{-4} mg/l [1)]
	algae	*Chlorella pyrenoidosa*	164hEC_{19}=0.1mg/l [1)] (Depression of population growth)
	insect	*Chironomus plumosus*	48hEC_{50}= 1mg/l(Immobilisation) [10)] 30dMATC=0.034mg/l(Immobilisation) [10)]

Environmental levels	Media	Fiscal year	Number of detections / number of samples	Range of detection	Limit of detection	Limit of quantitation
	water	1983	0/27 [9)]		(0.01) ng/l	-
	water	2003	25/36[9)]	nd~0.8 pg/l	(0.09) pg/l	(0.3) pg/l
	sediment	1983	0/27 [9)]		(0.0006 0.0 024) ug/g-dry	-
	sediment	2003	137/186[9)]	nd~1,500 pg/g-dry	(0.4) pg/g-dry	(2) pg/g-dry
	shellfish	2003	30/30[9)]	tr(1.6)~19 pg/g-wet	(0.81) pg/g-wet	(2.4) pg/g-wet
	fish	2003	70/70[9)]	tr(1.7)~25 pg/g-wet	(0.81) pg/g-wet	(2.4) pg/g-wet

	birds	2003	10/10[9)]	31~450 pg/g-wet	(0.81) pg/g-wet	(2.4) pg/g-wet
	air	2003 (warm season)	35/35[9)]	0.047~0.19 pg/m^3	(0.0028) pg/m^3	(0.0084) pg/m^3
	air	2003 (cold season)	34/34[9)]	0.024~0.099 pg/m^3	(0.0028) pg/m^3	(0.0084) pg/m^3

REFERENCES
1. IPCS ; "Environmental Health Criteria 44□MIREX"□□1984□
2. IPCS ; "Health and Safety Guide 39□ MIREX"□□1990□
3. ANON ; Dangerous Prop. Ind. Mater. Rep., 6(1), 2-8 □1986□
4. ANON ; Dangerous Prop. Ind. Mater. Rep., 7(5), 88-91 □1987□
5. IARC ; "IARC Monographe on the Evaluation of Carcinogenic Risks to Humans", 20, 283-301□2001□
6. Wayland J. Hayes, Jr. & Edward R. Laws, Jr. ; "Handbook of Pesticide Toxicology Vol.2", MIREX, 856-860 □1991□
7. US-EPA ; "Health Effects Assessment for Mirex", PB88-179908, 1-39 (1987)
8. Donald R. Skaar et al. ; Can. J. Fish Aquat. Sci., 38, 931-938 1981
9. Ministry of the Environment of Japan ; "CHEMICALS IN THE ENVIRONMENT " (http://www.env.go.jp/chemi/en/kurohon/index.html)
10. US-EPA ; "AQUIRE " (2002)
11. U.S.DHHS ; "NTP Technical report on the toxicology and carcinogenesis studies of Mirex (CAS No. 2385-85-5) in F344/N rats(Feed studies)", TR 313, U.S.DHHS (1990)

Description of toxicological properties of Mirex

The examination data are described in Japanese.
The examination data collected from relative document are summarized as follow.

i) Toxicological properties
(RfD) 0.2μg/kg/day
(Rat, 24-month oral repeated dose toxicity) hypertrophy of liver at 1mg/kg/day
(Mouse, Two-Generation Reproduction Toxicity Study) decreased development of litter at 5mg/kg and stopped breeding at 1.8mg/kg
(Rat, Two-Generation Reproduction Toxicity Study) decreased development of litter and viability index at 25mg/kg
(Rat, Teratogenicity) anomalous of organ at 6mg/kg
(Rat, Carcinogenicity) tumour at liver
(Rat, half life time) a few mouth

Another support document for toxicity
(RTECS)
LD50 Oral: 235mg/kg (Rat)
LD50 Ski : 800mg/kg (Rabbit)
LD50 Oral: 125mg/kg (Hamster)

(POPs)
http://www.pops.int/documents/background/assessreport/en/ritteren.pdf

Risk or hazard evaluation

The government of Japan anticipates that persistent and highly bio-accumulative chemical substances with long-term toxicity (e.g. PCBs) may cause irreversible environmental pollution and have adverse effects on human health or environment.
In order to prevent environmental pollution, the Chemical Substances Control Law stipulates that hazardous properties of chemicals should be checked based on the existing knowledge or by the tests which are consistent with the methods of the OECD Test Guidelines, conducted by the OECD GLP facilities.
If persistent and highly bio-accumulative properties with long-term toxicity are detected from chemical substances, they are classified as Class I Specified Chemical Substances and are subject to the final regulatory action (ban on manufacture, import, and use).