7.1.10 CHRONIC KIDNEY DISEASE OF UNKNOWN ETIOLOGY (CKD*u*) AND ARSENIC POISONING DUE TO ILLEGAL PESTICIDES

BACKGROUND

In recent years a significant increase in patients of Chronic Kidney Disease of unknown etiology (CKDu) has been observed in some parts of Sri Lanka, especially in Medawachchiya, Padaviya, Kebitigolawa, Medirigiriya (North Central Province), Nikawewa (North Western Province), Dehiattakandiya (Eastern Province) and Giradurukotte (Uva Province). Uniqueness of this disease is that its victims do not share the same history as other kidney patients who have had it either due to diabetes, high blood pressure, past snake bites or urinary tract infections. Etiology of this disease has since been attributed to a range of causes, including presence of the heavy metal cadmium in water that would potentially have introduced to water from inorganic fertilizer used in paddy fields, presence of excessive amounts of fluoride in drinking water and prevalent use of low quality aluminum utensils, presence of toxins produced by microorganisms such as cynobacteria in water. Despite the effort of about 60 researchers including those who were funded by WHO over the last decade, none of these hypotheses have been supported with evidence, in fact, the data available prove them not to be the cause. The causative factors and etiology of this chronic kidney disease therefore is still considered uncertain or unknown and abbreviated as CKDu with recommendations of the National Research Programme for CKD of the Ministry of Health in Sri Lanka.

Endemic occurrence of the disease was firstly recognized in the 1990s in certain areas of North Central Province, and this has been on the increase dramatically over a period of 10-15 years and Table 1 presents the registered number of CKDu patients in government hospitals and renal clinics in the respective disease affected areas.

Table 1: Number of patients reported at the end of 2010

Area	Number of patients
Anuradhapura	1800
Medawachchiya	2500
Padaviya	1300
Sri pura	500
Medirigiriya	600
Hingurakgoda	600
Polonnaruwa	900
Giradurukotte	2500
Nickawewa	500

There are also records that CKDu has reached epidemic proportions in the above mentioned parts of Sri Lanka, as the affected number of people is on an alarmingly steady increase over the years

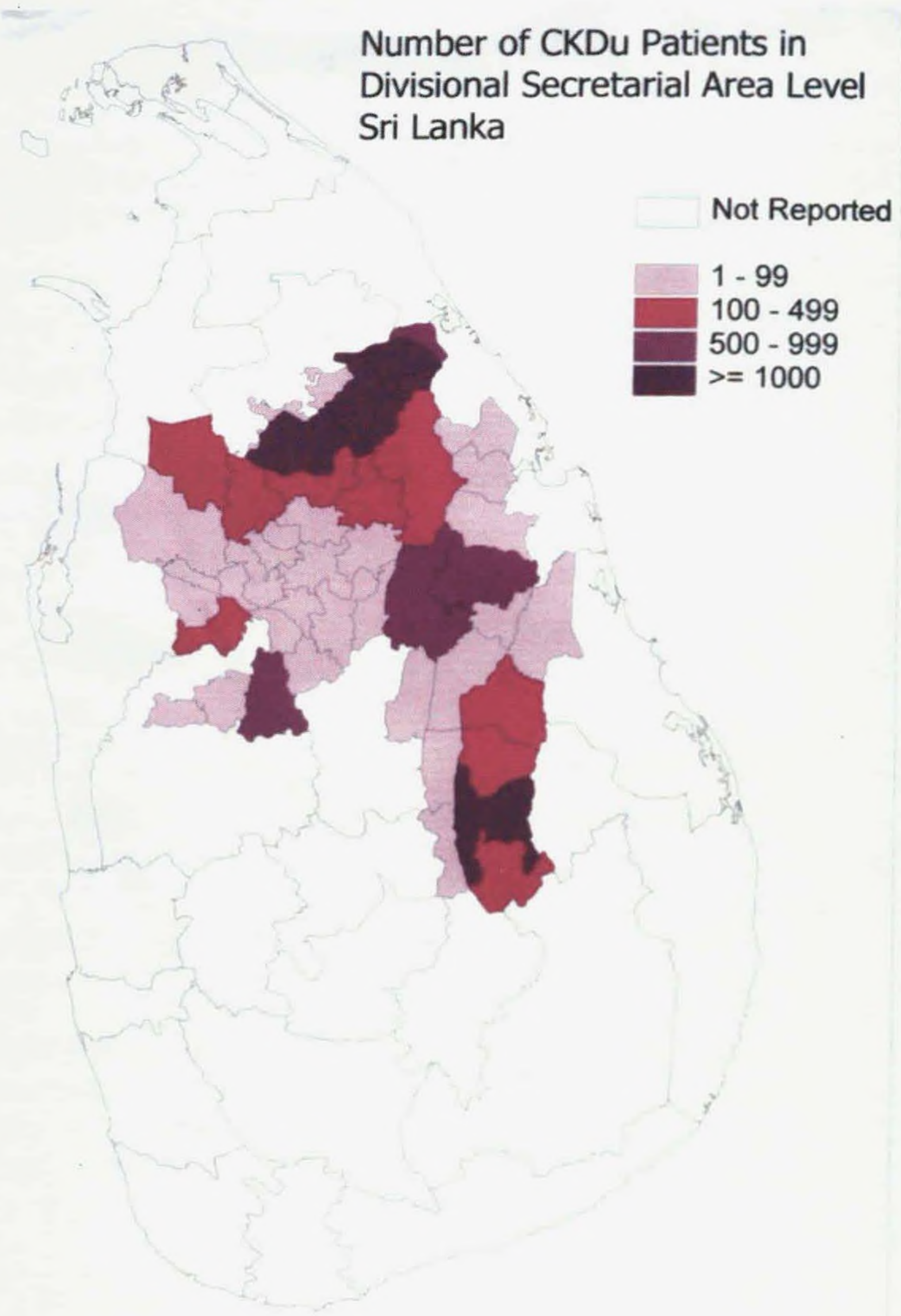

Fig. 2: Distribution of CKDu patients in Divisional Secretariat level

RECENT RESEARCH ON CKDu

Few months ago, a group that consists of university academics, medical doctors, mathematicians from relevant institutions commenced a new research with the intention of finding the causes and also treatment and prevention methods for this miserable disease.

THE INVESTIGATION GROUP

- **Prof.Nalin de Silva**- Dean, Science-University of Kelaniya
- **Prof.Priyani Paranagama**-Head-Chemistry-Uni. of Kelaniya
- **Prof.Mala Amarasinghe**- Head-Botany-Univ. of Kelaniya
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During the assessment of patients our group noticed hyper-pigmentation and keratosis in palms and soles of patients, a symptom characteristic for chronic **Arsenic** (As) poisoning (Plate 1)

Table 2 : Percentage dermal manifestation of chronic As poisoning symptoms observed in the sample of CKDu patients and with individuals of the control group.

Dermal manifestation	**Number of patients (n=125)**	**%**	**Number of individuals in control group (n=180)**	**%**
Hyper pigmentation of palms	56	44.8	34	18.8
Hyper pigmentation of soles	49	39.2	26	14.4
Keratosis of palms	29	23.2	19	10.5
Keratosis of soles	22	17.6	15	08.3

Plate1 : Keratosis and hyper-pigmentation of CKDu patients encountered in the study area

Accordingly, the percentage of CKDu patients who manifested chronic As poisoning symptoms were greater than that among the control group. Observation of these symptoms among the individuals of the control group however indicates that being inhabitants of the area who use the same water for drinking, have already bio-accumulated As, nevertheless to a lesser extent than those who have been diagnosed as CKDu patients, which means that they too will suffer with CKDu with continuous use of As contaminated groundwater. Most CKDu patients also manifest other clinical symptoms as presented in Table 3.

Other clinical symptoms observed among the subjects of the study	**CKDu patients(%)**	**Controls(%)**
Generalized body weakness	**95**	**35**
Headache	**91**	**44**
Burning of eyes	**84**	**12**
Nausia	**76**	**18**
Mild to moderate hepatomegaly and spleenomegaly	**25**	**04**
Epigastric pain	**63**	**16**
Paresthesia	**51**	**12**

Table 3: Other clinical symptoms manifested by CKDu patients in the study area.

Further we were able to detect other clinical features of chronic arsenic poisoning including generalized body weakness, headache, burning of the eyes, anaemia, nausea, hepatomegaly and spleenomegaly enlargement of liver and spleen), epigastric pain, paresthesia .

Table 4: Urinary As contents of CKDu patients and individuals of the control group

Urinary arsenic Concentration (ug/L)	**CKDu patients (%) (n=125)**	**Controls (%) (n=180)**
0-10	4.0	10.0
10-20	4.8	13.3
20-30	6.4	26.6
30-40	12.0	21.2
40-50	32.0	14.4
50-60	25.6	10.0
>60	15.2	4.5

Arsenic is having higher affinity to keratin. Hence comparatively higher concentration of arsenic has been observed in high keratin containing tissues such as hair and nails . In people with no known exposure to arsenic, the concentration of arsenic in hair is generally 0.02-0.2mg/kg (Valentine et al.1979,Narang et al.1987,Wang et al.1994,Kurttio et al.1998)). Hair samples of CKDu patients have been shown high amount of arsenic compared to that of individuals in the control. It further substantiates the chronic arsenic poisoning of CKDu patients in the study area.

Table 5: As content in hair samples of CKDu patients and individuals of the control group

Hair samples	**Arsenic -mg/kg**
Mean normal-unexposed	0.02 – 0.2
Control	**0.22** ±0.01
CKDu patients	**1.27**±0.22 to **7.03**±1.06

PRESENCE OF AS IN ORGANS OF DECEASED CKDu PATIENTS

Gross appearance of the kidneys of CKDu patients were observed during autopsy studies, to be granular, contracted and with marked cortical thinning. Average weight of CKDu affected kidneys were approximately 40-50 g when compared to a normal kidney that weighs about 125-150 g (Plate 2).

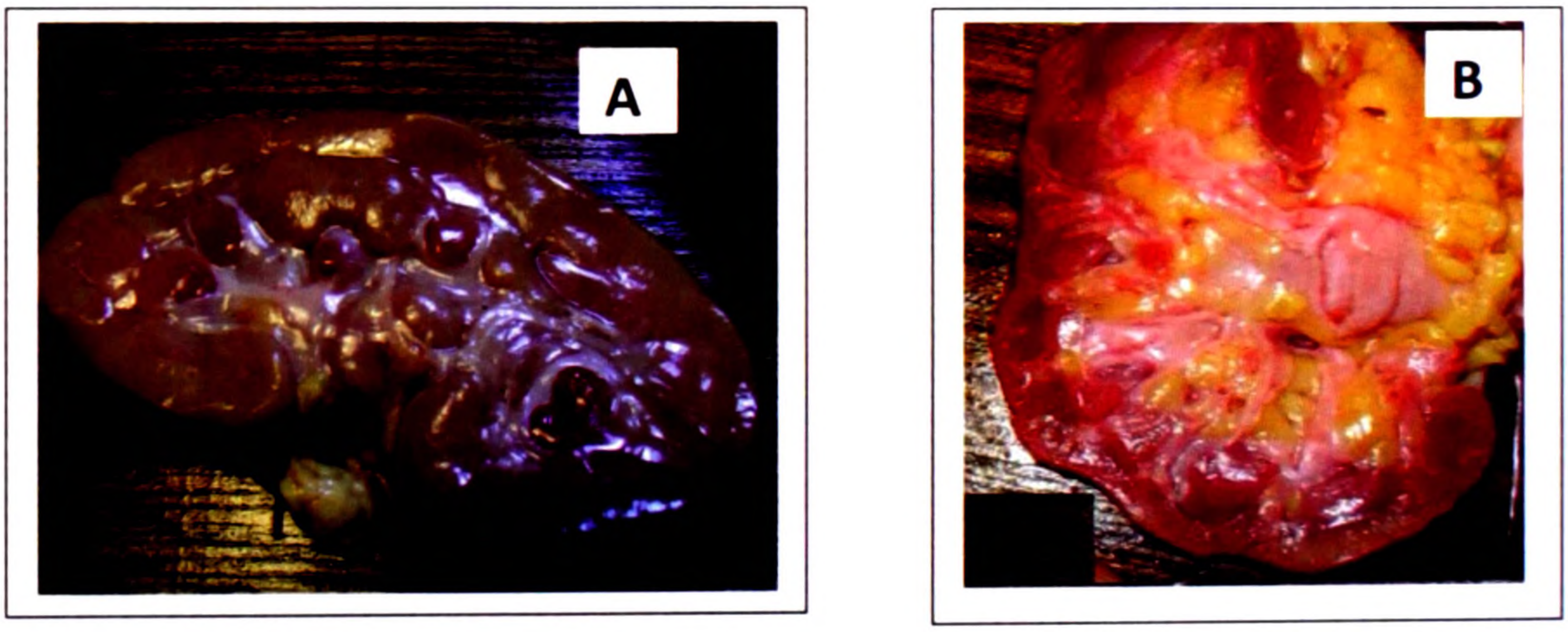


Plate 2: A cross section of a normal kidney (A) and CKDu affected kidney (B)

Kidney is the major route for the excretion of arsenic and its metabolites from the body and also it is the primary site of biotransformation of arsenic (Kalia et al-2007). It is reported that kidneys of individuals exposed to high levels of As have accumulated high amounts of it in their kidneys (Tchounwou-2003). Organ samples from deceased CKDu patients from the study area also have shown about ten-fold increase of arsenic in comparison to that of kidneys of an unexposed individual.

Table 6: Arsenic in organs from deceased CKDu patients from the study area.

Sample	Total Arsenic content (μg/kg)		
	Previous value recorded from normal individuals*	CKDu patients	
		Lowest value	Highest value
Large Intestine	20	189.5±25.6	292.3±50.2
Rectum	20	283.4±34.3	301.5±60.3
Liver	30	264.9±45.8	395.8±40.1
Thyroid	40	187.2±44.6	234.1±35.3
Spleen	20	255.6±65.5	273.6±33.9
Kidney	30	213.5±37.1	275.3±45.8

Above results reveal that CKDu patients have exposed to high concentrations of As in their environments.

HISTOPATHOLOGICAL ANALYSES ON RENAL TISSUES OF DECEASED CKDu PATIENTS

Kidney tissue samples from deceased CKDu patients were further analysed using H & E histopathological staining method. Density of Bowman's capsules in the cortical region of CKDu affected kidneys was conspicuously lower than that of a normal kidney (Plate 3) as previously observed with kidneys affected by tubulointerstitial disease.

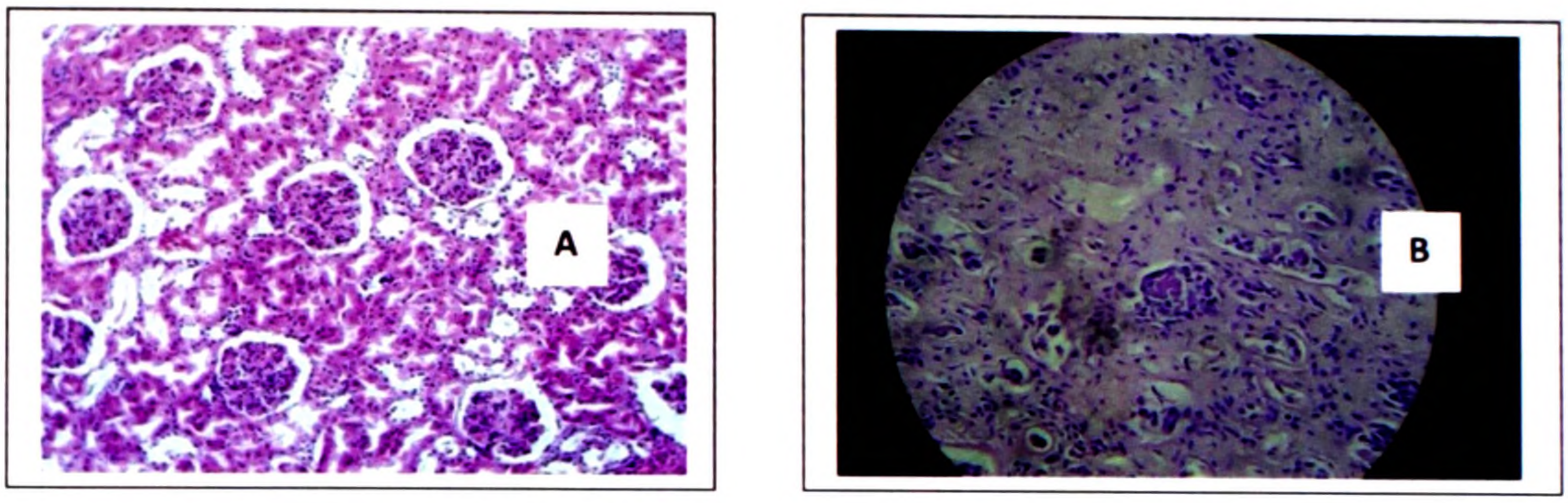


Plate 3: Cross section of the cortex of (A) normal kidney (B) CKDu affected kidney

Observations made with CKDu affected kidney tissues stained with Von Kossa staining revealed the presence of calcium in them. Metallic silver areas were observed under microscope where Ca deposits are present (Plate 4).

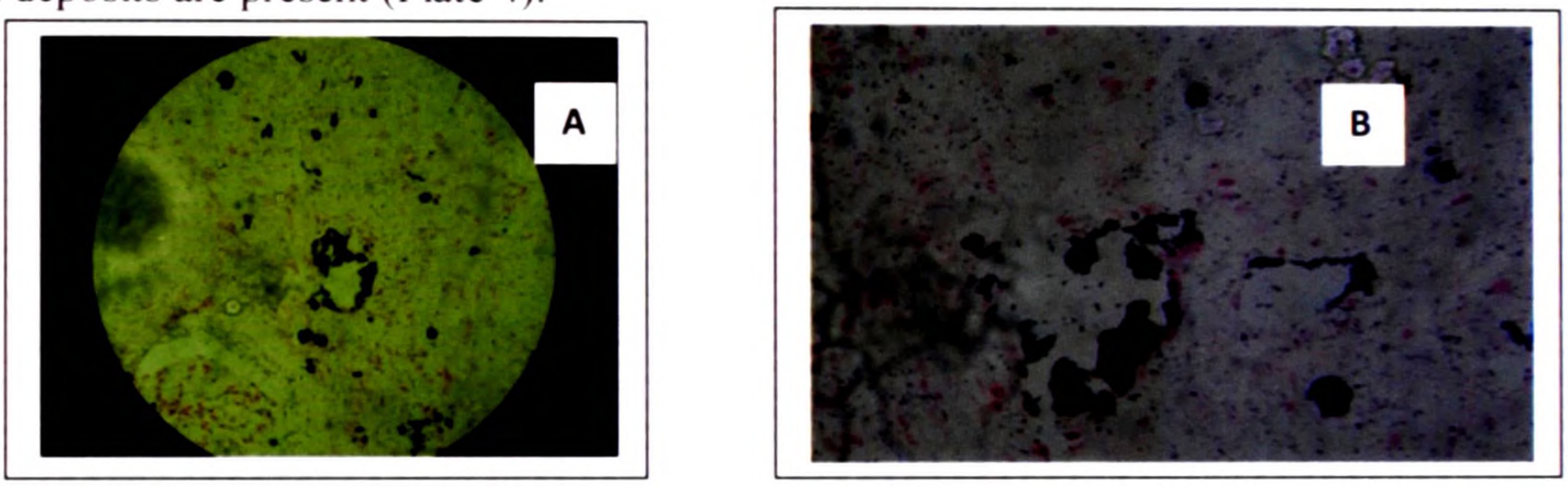


Plate 4: Cross section of the cortical region of a CKDu affected kidney (A). Enlarged view of a Bowman's capsule deposited with calcium (B).

CKDu affected kidney tissues stained with copper sulphate reveled the presence of arsenates in them as areas of characteristic paris green colour (Plate 5).

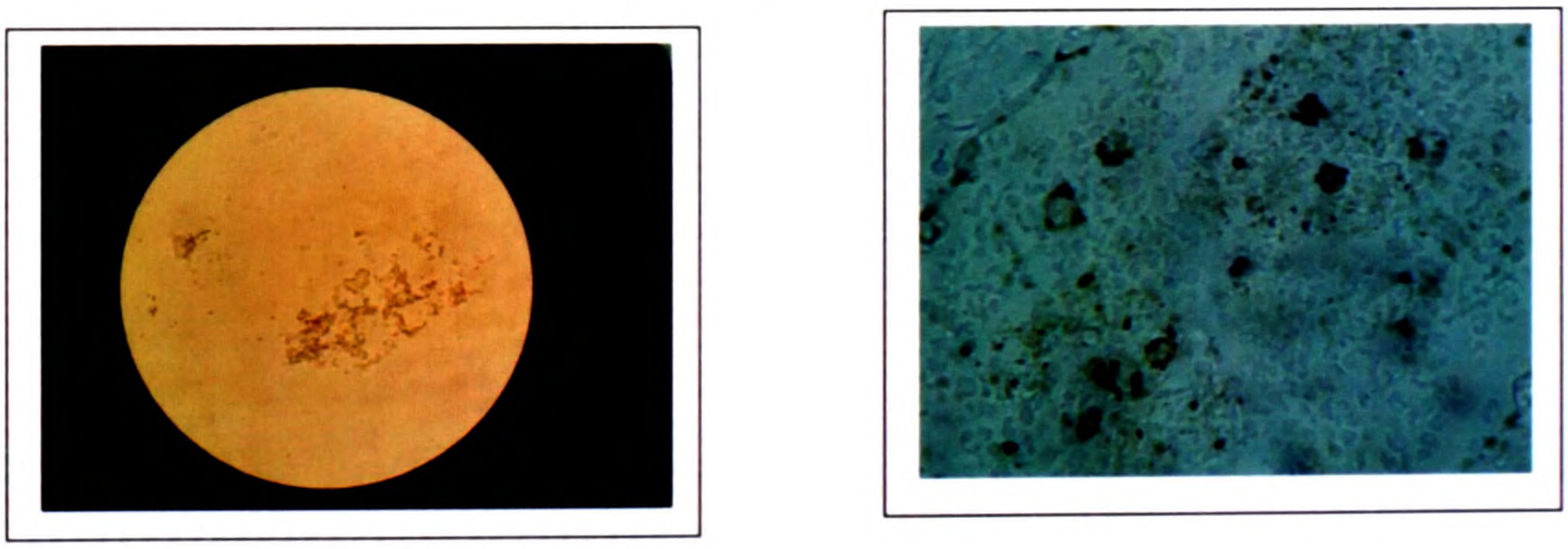


Plate 5: Part of a CKDu affected kidney tissue. Dark patches are the areas appear in Paris green colour under light microscope.

ARSENIC IN DRINKING WATER

These observations have led us to analyze drinking water of patients for Arsenic and these analyses were carried out in the analytical chemistry laboratories at University of Kelaniya and Water Recourses Board in Colombo 07. Surprisingly we were able to detect abnormally high amounts of Arsenic and Mercury in our water samples which are well beyond WHO (World Health Organization) permissible values (Table 7).

Table 7: Maximum permissible content of Arsenic in drinking water and the content observed in Drinking water of CKDu patients in Mahawilacchiya and Padaviya areas

	WHO upper limits in drinking water	Concentration in drinking water sources of CKDu patients
Arsenic	10 ug/L	20-200 ug/L

Chronic Arsenic poisoning is a severe crisis in State of Bengal inIndia and Bangladesh. It has been identified as the worst chemical disaster in human history. In Bangladesh, drinking As contaminated water and rice are the main sources of Arsenic in human bodies.

ARSENIC IN SRI LANKAN RICE

Chandrajith and his team in 2010 have identified relatively high amounts, ranging from 100 – 260 micro grams (ug) of Arsenic in rice that have been collected from CKDu endemic regions (Giradurukotte and Nickawewa but they have not correlate the findings with disease prevalence.

Table 8: Previous studies on Arsenic levels of rice in Sri Lanka

Year	**Principal author**	**Arsenic level (µg/kg)**
2004	Jayasekara, et al.	34-92
2008	Yamily, et al.	30-150
2010	Chandrajith, et al.	90-260

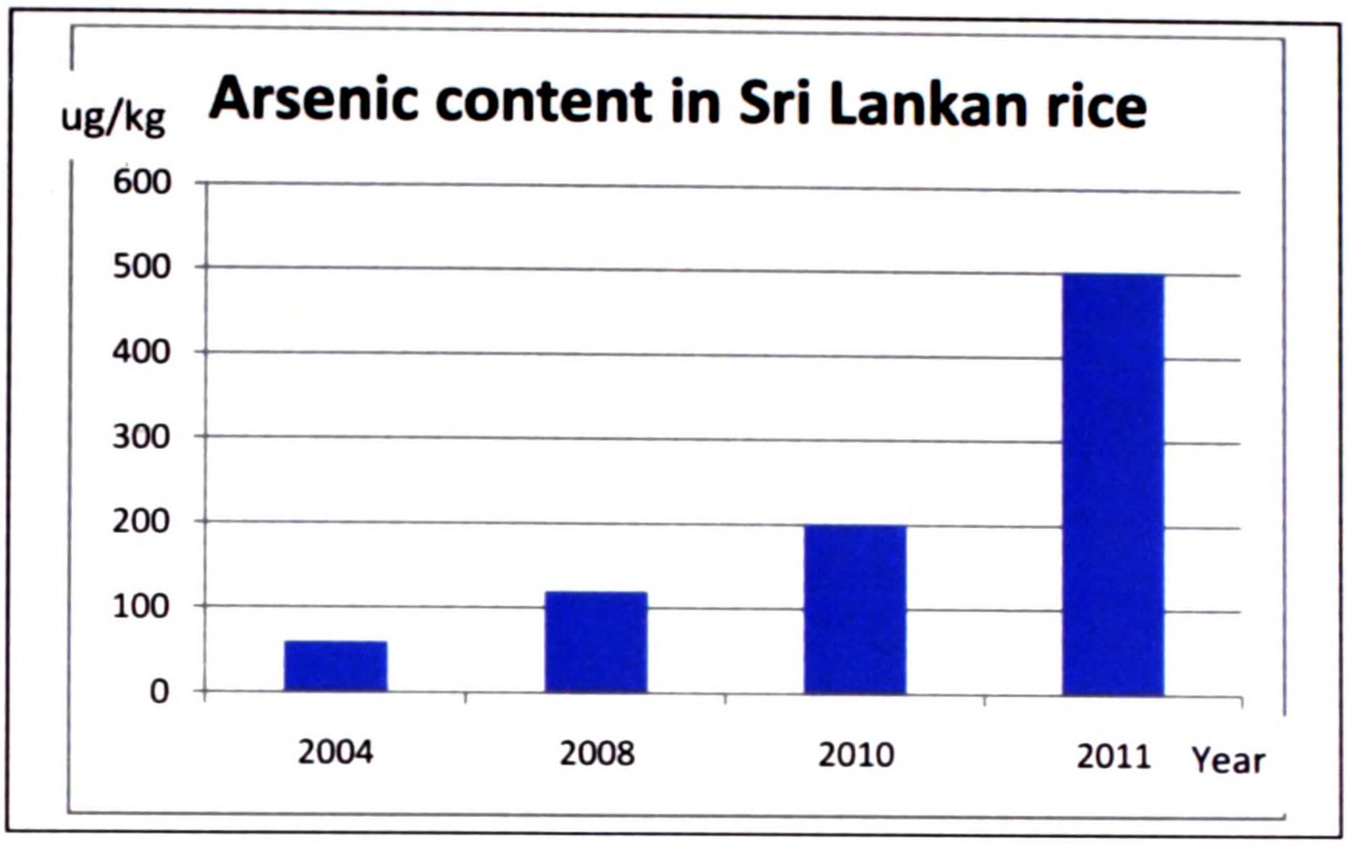


Fig. : Variation of Arsenic levels in Sri Lankan rice (μg/kg) from 2004 to 2011

As content of rice samples collected from the study area and outside are presented in Table 9 and the data are compatible with those that have been reported for Sri Lankan rice cultivars.

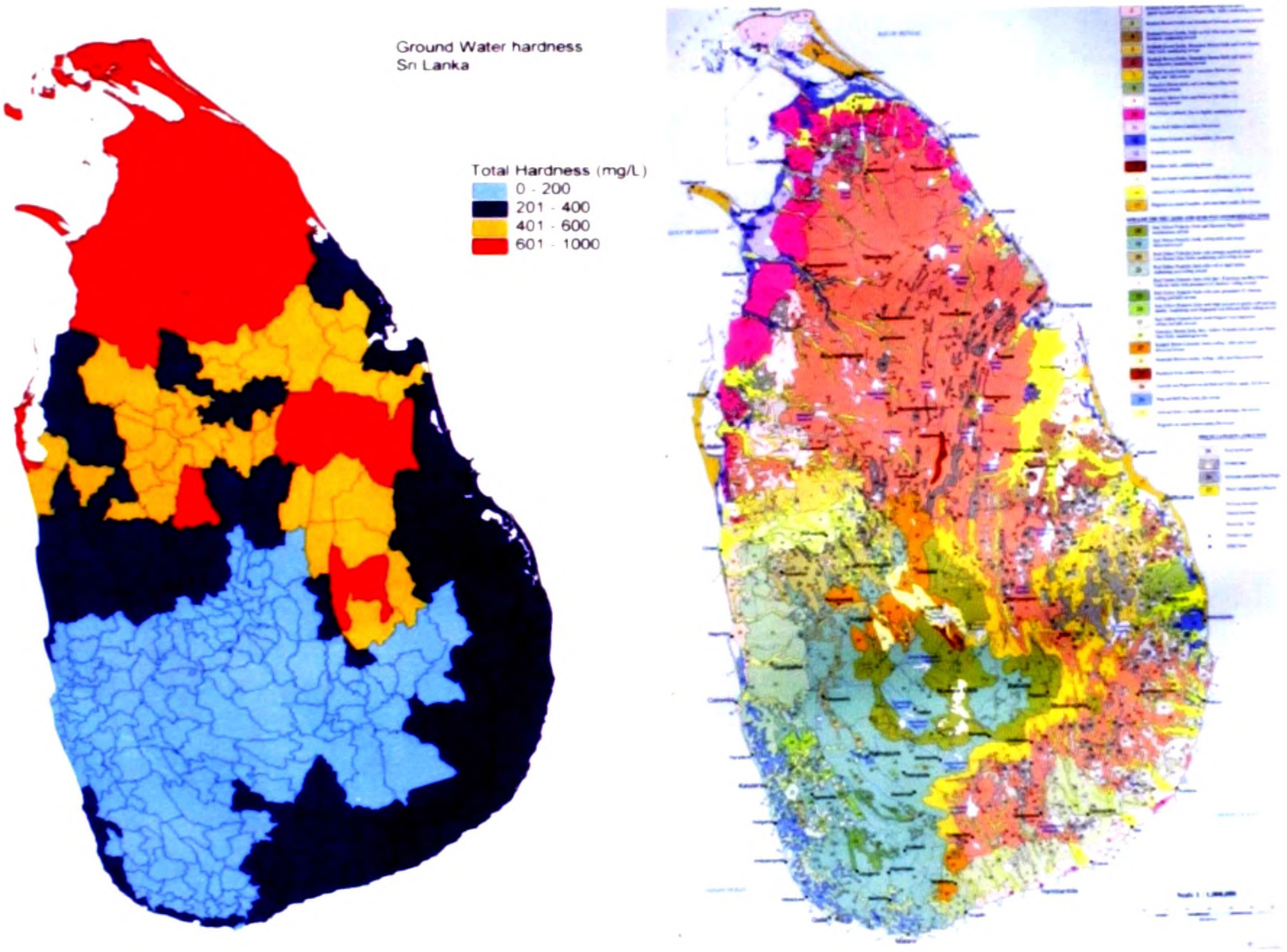
Table 9: Arsenic content in rice samples collected from the study area in Sri Lanka

Region	No of samples	Arsenic lowest value(μg/kg)	Arsenic highest value (μg/kg)
Padaviya	16	75.5 ±5.5	897 ±21.3
Sripura	12	67.3 ±4.9	995 ±14.5
Mahawilachchiya	14	33.2 ±3.9	1074 ±12.8
Mihinthale	10	28.6 ± 2.5	808 ±27.3
Kurunegala	12	28.5 ±2.8	656 ±5.4
Monaragala	10	95 ±7.5	435 ±4.6
Gampaha	10	36.4 ±6.8	585 ±5.5

RELATIONSHIP BETWEEN PREVALENCE OF CKDu AND GROUND WATER HARDNESS

We also observed that the number of CKDu patients observed had a marked positive relationship to the extent of ground water hardness, i.e. higher the ground water hardness, more the number of patients encountered in those areas (Fig. 3).

Also it was observed that Arsenic was present in higher concentrations in the hard water of a certain type of soil in that part of the country which are reported to have a high heavy metal retention capacity due to their chemical unique properties (Cation exchange capacity).



(A) (B)

Fig. 3: Geographical distribution of CKDu patients has shown a correlation with ground water hardness and soil type.

- (A) – Map of hardness of ground water in Sri Lanka
- (B) - Distribution of different soil types in Sri Lanka

Hard water areas coincided with the soil types represented in pale red colour in Map (B).

Difficulty in detecting Arsenic in water

Arsenic form strong bonds with Calcium and therefore they are not easily detectable in hard water. The conventional analytical methods used for soft water therefore were not suitable to detect Arsenic in hard water. This may be the reason why most of the time other investigators have not detected presence of Arsenic in water collected from CKDu-endemic areas. High Arsenic retention capacity of dry zone soils also would have contributed to this situation.

POTENTIAL SOURCE OF ARSENIC

Use of pesticides has already been identified as a risk factor for CKDu *(Wanigasuriya et al 2007)*. Logically, we have investigated pesticides for Arsenic as well as Mercury and our alarming results are presented below (Table 10)

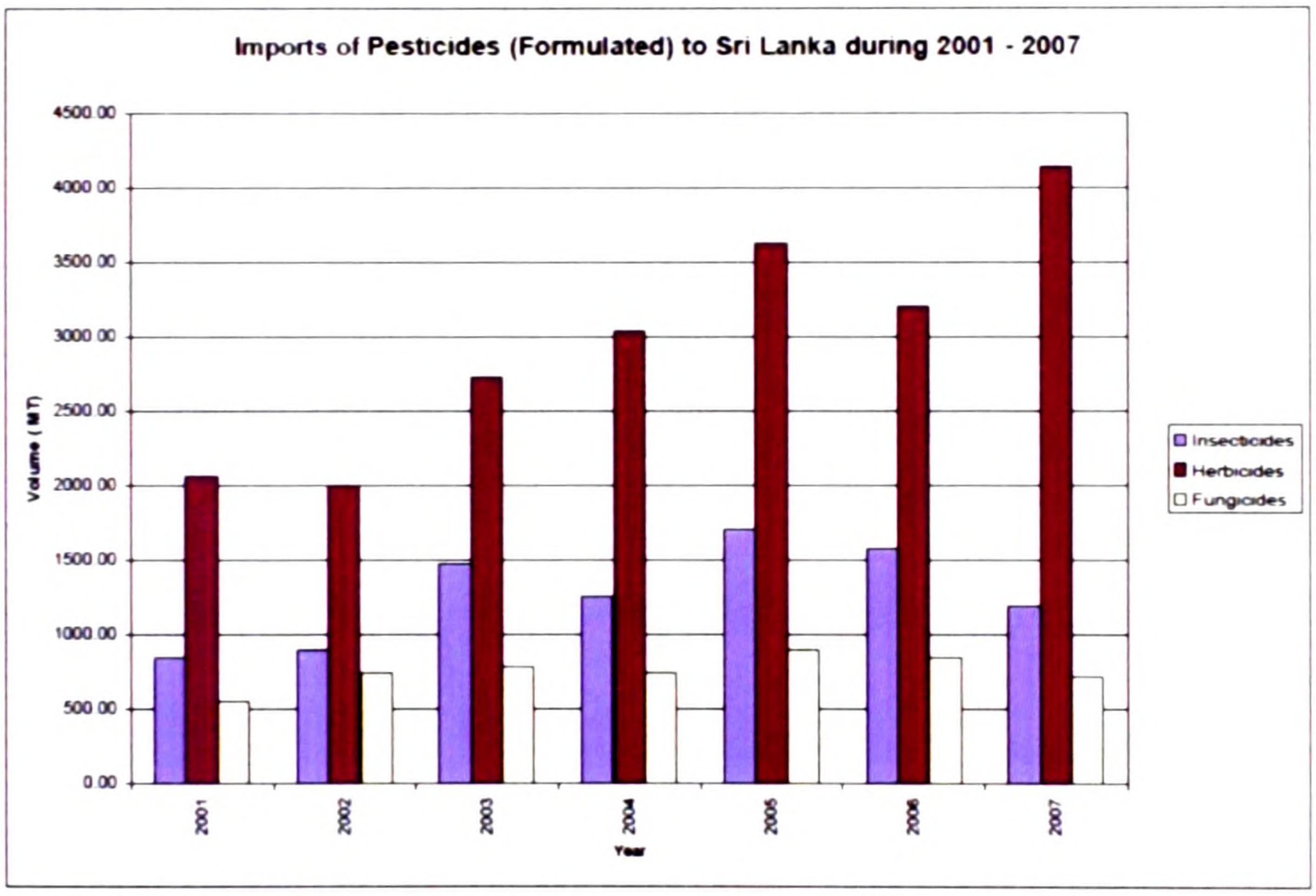
Table 10: Amount of Arsenic detected in major brands of pesticides and herbicides abundantly used in Sri Lanka

NO	Trade Name	Company	Type	As concentration(ug/L)
01	Round Up	Lankem	weedicide	496
02	Bassa	Lankem	Insecticide	318
03	Basudine 50 EC	Lankem	Insecticide	327
04	Evisect	Lankem	Insecticide	1097
05	Lannate	Lankem	Insecticide	1647
06	Nomini	Lankem	Weedicide	721
07	Pyrinex	Baurs	Insecticide	509
08	Ekalux	Baurs	Insecticide	1210
09	Lebaxid	Bayer	Insecticide	126
10	Provado	Heylis	Insecticide	452
11	Ricestar	Heylis	Weedicide	593
12	Mimiczo	Heylis	Insecticide	216
13	Selecron 50 EC	Heylis	Insecticide	297
14	Folicur EW	Heylis	Fungicide	412
15	Mancozeb	Heylis	Fungicide	700
16	Agromat EC 40	Heylis	Insecticide	575
17	Haydol M 60	Heylis	weedicide	1908
18	Accurator	Heylis	Insecticide	323
19	Captal	Hacros	Fungicide	1289
20	Calcran	Hacros	Insecticide	674
21	Trebon	Hacros	Insecticide	757
22	Powermate	Agrochem	weedicide	652
23	Solito	CIC	weedicide	615
24	Chikara	opexagro	Insecticide	291

25	Kemsan 50	Sunagro	Insecticide	1279
26	Marshal 20 SC	FMC	Insecticide	1197
27	Tiller Gold	Harrisons	Weedicide	2457
28	Quick	Harrisons	Insecticide	2782

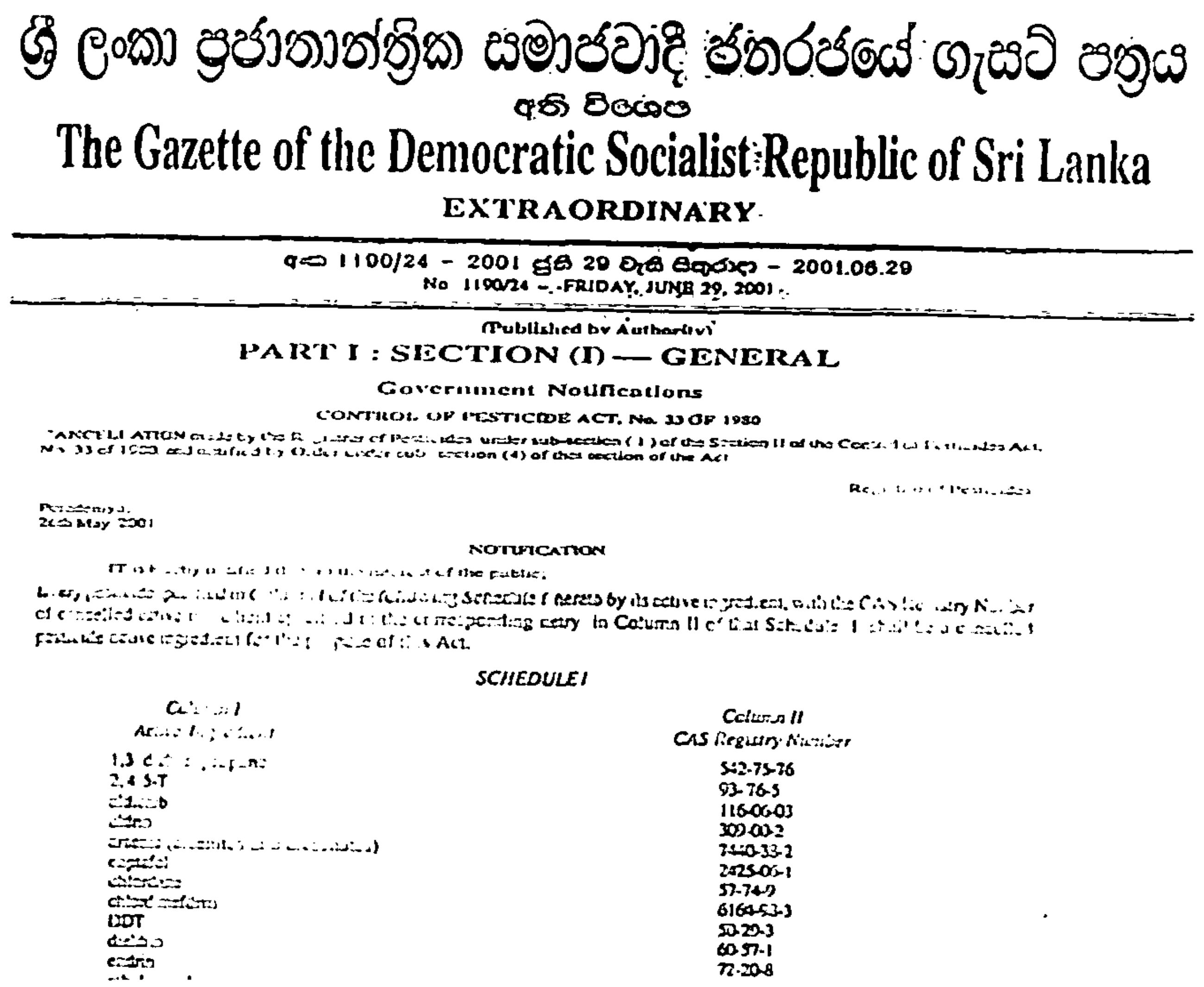
INCREASE OF PESTICIDE USAGE IN SRI LANKA

Amounts of pesticides, i.e. insecticides, herbicides and fungicides imported and uses in Sri Lanka are on the increase as presented in the following graph.



According to the provisions of the Control of Pesticides Act No 33 of 1980, importation and distribution of pesticides containing Arsenic and Mercury are among the prohibited acts and it has been notified with the Gazette Extraordinary (No 1100/24) on the 29th June 2001.

We therefore bring to your kind notice that although importation and distribution of Arsenic and Mercury containing pesticides is illegal in Sri Lanka they are being freely made available for our farmers.



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No 1190/24 - FRIDAY, JUNE 29, 2001

(Published by Authority)

PART I : SECTION (I) — GENERAL

Government Notifications

CONTROL OF PESTICIDE ACT, No. 33 OF 1980

CANCELLATION made by the Registrar of Pesticides under sub-section (1) of the Section 11 of the Control of Pesticides Act, No. 33 of 1980 and notified by Order under sub-section (4) of that section of the Act

Registrar of Pesticides

Peradeniya,
2[illegible] May 2001

NOTIFICATION

IT is hereby [illegible] of the public;

Every pesticide [illegible] in Column I of the following Schedule I hereto by its active ingredient, with the CAS Registry Number of cancelled active [illegible] the corresponding entry in Column II of that Schedule I shall be a cancelled pesticide active ingredient for the purpose of this Act.

SCHEDULE I

Column I Active Ingredient	Column II CAS Registry Number
1,3 dichloropropene	542-75-76
2,4 5-T	93-76-5
aldicarb	116-06-03
aldrin	309-00-2
arsenic ([illegible])	7440-33-2
captafol	2425-06-1
chlordane	57-74-9
chlordimeform	6164-53-3
DDT	50-29-3
dieldrin	60-57-1
endrin	72-20-8

NATIONAL IMPORTANCE OF THE PESTICIDE ISSUE

Chronic kidney disease is not the only problem associated with chronic Arsenic poisoning. There are many long standing non communicable diseases associated with chronic Arsenic poisoning and they include,

- Cancers
- Ischemic Heart Diseases
- Cerebro Vascular Diseases-Strokes
- Diabetes Mellitus
- Gastritis
- Low immunity for viral fevers

Not only arsenic it is reported that considerably high amount of cyanide and mercury contain in pesticides available in Sri Lanka.

Effects of Chronic cyanide toxicity

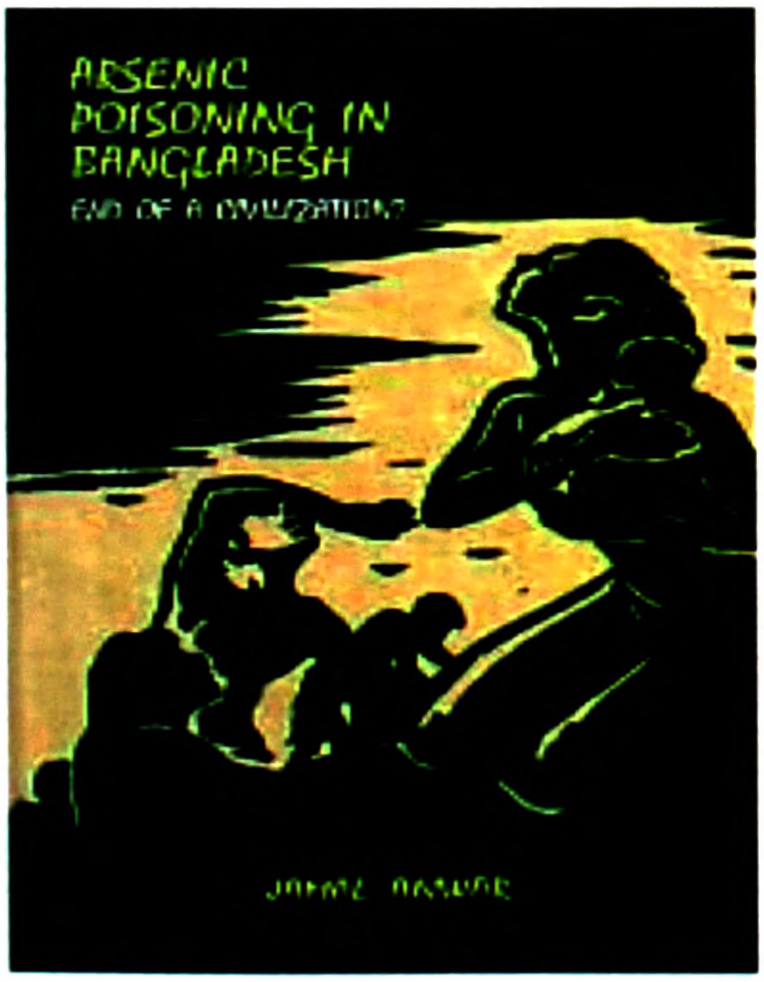
- Polyneuropathy
- Visual defects
- Hypothyroidism
- Abortions

Effects of low dose mercury toxicity

- Decrease motor functions, visual and auditory functions
- Disruption of attention and memory
- Infertility
- Chronic renal failure
- Developing nervous system of the fetus is sensitive to even several micrograms of mercury.
- Mothers consuming diet containing mercury pass the toxicant to foetus and to infants through breast milk.

Since tons of pesticides have been used in Sri Lanka for the last 20-25 years, Arsenic,Mercury, Cyanide in them may potentially be the cause for rapidly increasing prevalence of heart disease, diabetes and cancer in Sri Lanka, curing for which the Sri Lankan Government allocates substantial resources annually.

In Bangladesh half of the total population of 143 million is subjected to chronic arsenic poisoning. It is estimated more than 60 million of Bangladesh population are suffering with Diabetes mellitus. According to Bangladesh renal association more than 20 million people are suffering from chronic kidney disease and it claim more than 40000 lives per annum. **Jamal Anwar** a Bangladesh scientist says this disaster is due low quality agro chemicals which have been imported to country for last 3 decades.



"Arsenic Poisoning in Bangladesh- end of a Civilization"

Do you wait until the same thing is happened to Sri Lanka?