ANNUAL REPORT OF THE MALAYSIAN ADVERSE DRUG REACTIONS ADVISORY COMMITTEE 2004

1. **MADRAC MEMBERS**
Members of the Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) were as follows:

MADRAC Members/(Alternate members)

Y. Bhg Datin Hjh. Hasiah Abdulah
Director of National Pharmaceutical Control Bureau.Ministry of Health Malaysia
Chairperson

Dato Dr Hj Abdul Aziz b Abdullah/(Dr. Sarfraz Manzoor Hussain)
Consultant Psychiatrist, Hospital Kuala Lumpur
Committee Member

Puan Sri Dr Suraiya H. Hussein/(Dr. Gangaram Hemandas)
Consultant Dematologist, Hospital Kuala Lumpur
Committee Member

Tan Sri Dato Dr R. P. Lingam
Representative of the Malaysian Medical Association.
Committee Member

Prof C.T. Chua
Consultant Nephrologist, Medical Faculty, University Malaya.
Committee Member

Prof Madya Dr Rahmat b Awang/(Dr. Abdul Fatah Hj. Abdul Rahman)
National Poisons Centre, Universiti Sains Malaysia.
Committee Member

Prof. Dr. Nik Aziz b Sulaiman/(Prof. Dr. Ima Nirvana Soelaiman)
Clinical Pharmacologist Medical Faculty, Universiti Kebangsaan Malaysia.
Committee Member

Dr G.R. Letchuman Ramanathan/(Dr. Patmini Menon)
Consultant Physician, Hospital Ipoh.
Committee Member

Dr. S Ganeshnathan
Consultant Physician, Hospital Kuala Lumpur.
Committee Member

Dr. Mardziah Alias/(Dr. Norzila Mohamed Zainudin)
Consultant Paediatrician, Hospital Kuala Lumpur
Committee Member

Pn Hasnah Ismail / (Pn. Rosminah Mohd. Din)
Head of Assistant Director, Pharmaceutical Services Division, Ministry of Health.
Committee Member

Pn Eishah Binti A. Rahman
Secretary, Drug Control Authority, Ministry of Health
Committee Member

Puan Abida Syed Haq
Head, Centre for Post Registration, NPCB, Ministry of Health
Secretary

2. **MEETINGS**
The committee met six times over the year and a total of 1500 adverse drug reaction reports were reviewed.

Meeting	77 01/04	78 03/04	79 05/04	80 07/04	81 09/04	82 12/04
No of Reports	173	169	284	255	280	339

3. ANALYSIS OF ADR REPORTS
A detailed review and analysis of the ADR reports received during the year 2004 was conducted (Ref: Appendix 1)

4. REGULATORY ACTIONS
4.1 During the course of the year, the following recommendations were proposed by MADRAC and accepted by the Drug Control Authority (DCA):

	PRODUCTS	**REGULATORY ACTIONS IMPLEMENTED**	**DCA MEETING**
1.	Cisapride	i. To cancel the registration of products containing Cisapride. ii. Allow exemption to supply on a named patient basis products containing cisapride that were previously registered by the the DCA iii. Giving 6 month period of time from the date of DCA approval for the product holder to withdraw all the product that already registered and marketed in Malaysia.	*DCA 156*
2.	*Comfrey* and *Senecio spp*	i) To cancel the registration of all products containing *Comfrey* and *Senecio spp* as both of these herbs contain unsaturated pyrrolizidine alkaloids (PA) which are considered to be hepatotoxicity and hepatocarcinogens. ii. Grant a 6-month grace period for the product registration holders to withdraw all the products that have already been registered from the Malaysian market	*DCA 156*
3.	Terfenadine	i. Cancel the registration of all products containing terfenadine in view of the association of cardiac adverse events arisisng from the use of terfenadine ii) Grant a 6-month grace period for the product regsitration holders to withdraw all the products that have already been registered from the Malaysian market	*DCA 158*
4.	Nimesulide	In view of the findings of the review of nimesulde by the European Medicines Evaluation Agency, it was	*DCA 159*

		recommended that i. The earlier suspension on the registration on products containing nimesulide be withdrawn with the condition that dosage is limited to a maximum of 100mg twice a day. ii) The indication for oral products be restricted for: o Treatment of acute pain o Symptomatic treatment of painful osteoarthritis. o Primary dysmenorrhea. iii) All product registration holders notify health care professional on the restriction on indications, new maximum dose and contraindications in order to minimize the risk of hepatotoxicity.	
5.	Atypical Antipyschotic Agent	To add a warning pertaining to the potential hyperglycemic effect ssociated with the use of Atypical Antipyschotic Agents: a. Clozapine b. Olanzepine c. Risperidone d. Quetiapine e. Ziprasidone f. Aripiprazole The warning that DCA agreed to put in the package insert are : ***WARNINGS*** ***Hyperglycemia and Diabetes Mellitus*** ***Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical***	*DCA 160*

		antipsychotics are not available. ***Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.***	
6	Antidepressants	The inclusion of the following warning statement in the product inserts of all products indiacted for the treatment of depression: ***Suicidality in Children and Adolescents*** • *Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with* ***major depressive disorder (****MDD) and other psychiatric disorders.* • *Anyone considering the use of an antidepressant in a child or adolescent for any clinical use must balance the risk of increased suicidality with the clinical need.* • *Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.* • *Families and caregivers should be advised to closely observe the patient and to communicate with the prescriber.* • *A statement regarding whether the particular drug is approved for any pediatric indication(s) and, if so, which one(s).*	*DCA 165*

4.2 Review of Periodic Safety Update Reports (PSURs)

Over the year, the Periodic Safety Update Reports (PSURs) submitted by the industry for the New Chemical Entities registered by the DCA were reviewed and where necessary, the product registration holders were instructed to update the package inserts to reflect new safety data and findings.

5. ACTIVITIES

MADRAC members conducted several talks over the year in an effort to promote ADR reporting as well as to update health professionals on issues related to drug safety

NO.	TITLE OF PRESENTATION	FORUM	PLACE & TIME
1	Factors for Success in Pharmacovigilance	11th ICDRA, Madrid, Spain (under the auspices of WHO	19 Feb 2004 Madrid, Spain
2	Safety Surveillance of Cosmetics	Seminar organised by CTFA & BPFK (for the Cosmetic Industry)	Mar 2004 Petaling Jaya
3	Monitoring Safety Of Dietary Supplements	Seminar organised by the Direct Selling Association of Malaysia	29 Mar 2004 Petaling Jaya
4	ADR Monitoring: Getting the Facts Right	Seminar for Hospital Pharmacists on Erythropoeitin	17 April 2004 Kota Kinabalu Sabah
5	Peranan Kakitangan Sokongan dalam Pemonitoran ADR	PTK4 Kumpulan Sokongan, KKM	23 Apr 2004 Bangsar, KL
6	ADR Monitoring – CME session	Hospital Seremban	24 Apr 2004
7	ADR Monitoirng – Pre & Post Registration	19th Scientific Meeting of the Malayisan Society of Pharmacology and Physiology	18 May 2004, UMMC, KL
8	Food Supplements – Do we really need them?	Forum organised by Family Health Division, MOH	13 July 2004, KL
9	Studies on Adverse Drug Reactions to Traditional Medicines	Seminar R& D Farmasi	7 September 2004, Sepang
10	Pharmacovigilance Planning: Impact on Non-ICH Countries	Annual Conference, International Society for Pharmacovigilance	7 October 2004, Dublin, Ireland
11	Monitoring of Adverse Drug Reactions	Continuous Education for Pharmacist	9 October 2004, Kuantan, Pahang
12	Monitoring of Adverse Drug Reactions	CME Hospital Taiping	27 November 2004, Taiping Perak
13	Training Session for Hospital Pharmacists (Perak) in Monitoring ADRs	Hospital Taiping	27 November 2004, Taiping Perak
14	Adverse Drug Reaction Monitoring	CME Hospital Kuala Pilah	3 December 2004, Kuala Pilah Negeri Sembilan.
15	Farmakovigilans: Tanggungjawab Professional Ahli Farmasi	Seminar untuk Pegawai Farmasi U48	8 December 2004, Kuantan
16	Monitoring of Adverse Drug Reactions – CME session	CME Hospital Kangar	11 December 2004 Kangar, Perlis

6. WORLD HEALTH ORGANISATION

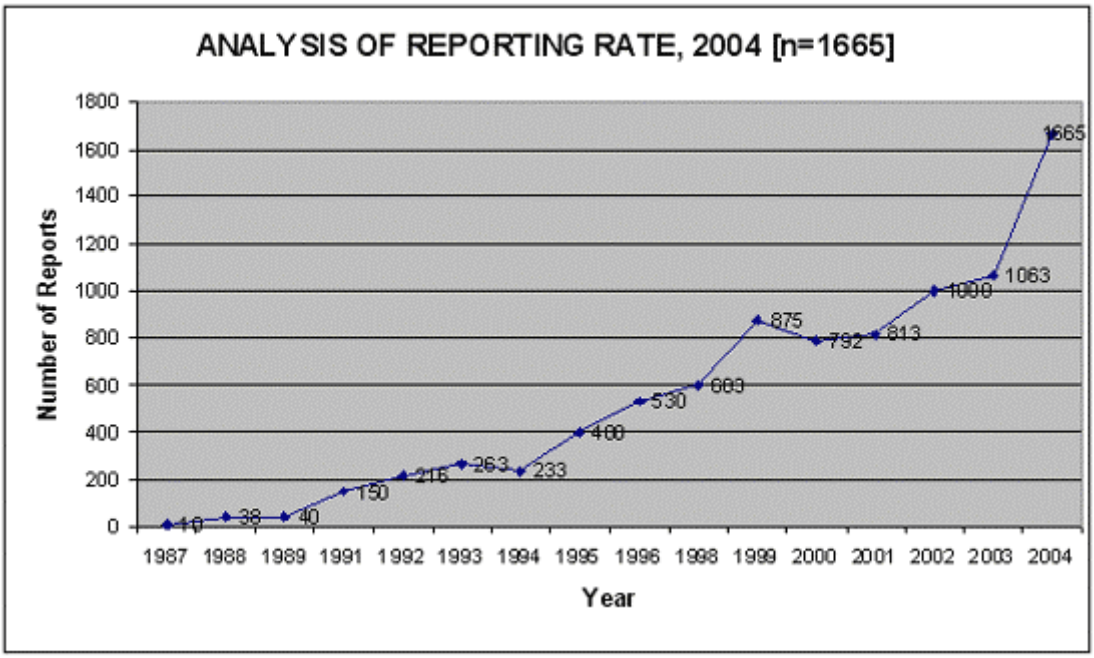
1454 ADR reports reviewed by MADRAC were submitted to the International Centre for DRUG Monitoring (WHO) in Upssala, Sweden.

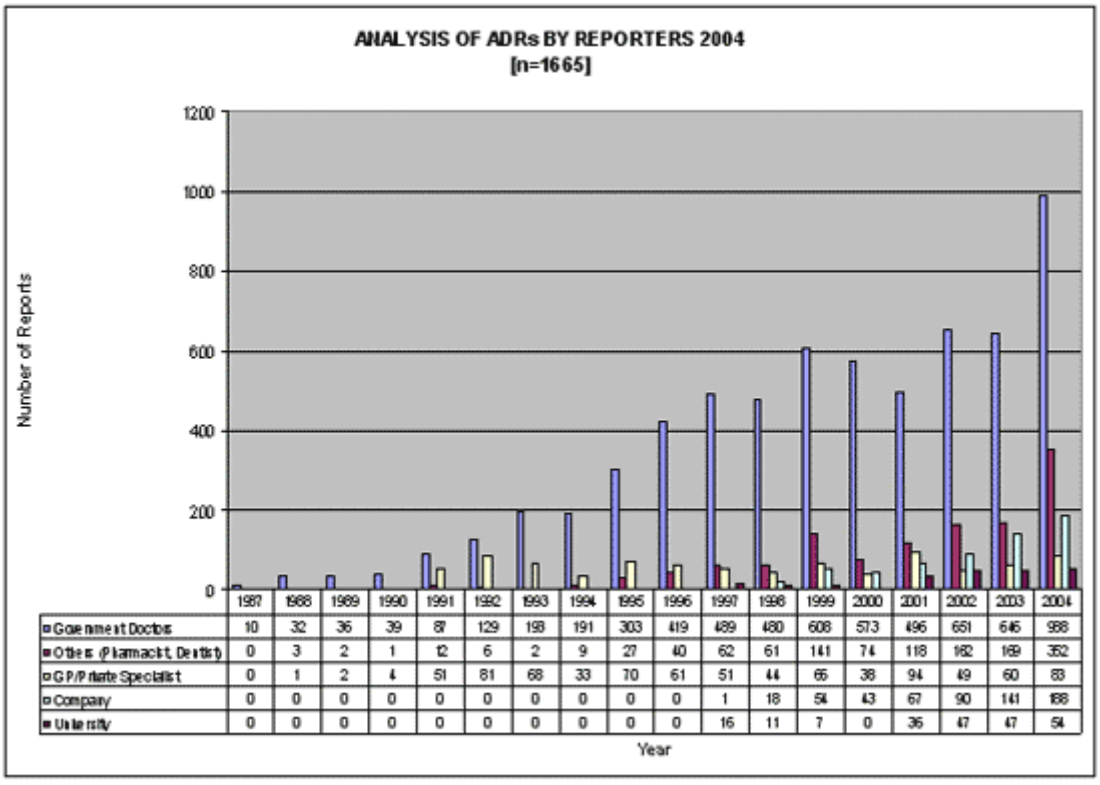
ANALYSIS OF ADR REPORTS RECEIVED WITH FATAL OUTCOME

Drug	ADR	Assesment
Allopurinol	Toxic Epidermal Necrolysis (2 cases)	Died – drug may be contributory
Zithromax	- Anaphylactic reaction - Heart block - Hypotension - Bradycardia	Died – drug may be contributory
Rofecoxib	- Heart attack	Died – drug may be contributory
Valdecoxib	- Myocardial Infarction - Dyspnea - Malaena	Died – drug may be contributory
Indomethacin	- Renal function abnormal	Died – drug may be contributory
Diclofenac	- Anaphylactic reaction	Died – drug may be contributory
Phentermine	- Tachycardia ventricular	Died – drug may be contributory
Lamotrigine	- Hepatorenal failure - Fever - Jaundice - Rash erythematous - Somnolence	Died – drug may be contributory
Gentamicin	- Renal failure acute - Renal impairment - Fever	Died – drug may be contributory
Losartan / Hydrochlorothiazide	- Oedema dependent - Hyponatremia	Died – drug may be contributory
Amlodipine	- Jaundice	Died – drug may be contributory
Ticlopidine	- Pharyngitis - Neutropenia - Sepsis - Liver Failure	Died – drug may be contributory

	- Renal function abnormal - Leucopenia - Nausea - Vomiting	
Timolol (Blocadren Tablet)	- Anaphylactoid reaction	Died – drug may be contributory
Gadopentetate Dimeglumine	- Renal failure chronic	Died – drug may be contributory
Mefenamic Acid	- Epidermal Necrolysis	Died – drug may be contributory
Lamivudine	- Hepatitis (2 cases)	Died – drug may be contributory
Fluconazole	- Medicine ineffective	Died – drug may be contributory
Fondaparinux (Arixtra)	- Dyspnoea	Died – drug may be contributory
Imatinib	- Paraplegia	Died – drug may be contributory
Win – EPA Capsule (Fish Body Oil)	- Acute liver failure	Died – due to adverse drug reaction
Methylenedioxy - methamphetamine	- Anaphylactoid reaction	Died – due to adverse drug reaction

APPENDIX 1


ANALYSIS OF REPORTING RATE, 2004 [n=1665]
Number of Reports
Year
1800
1600
1400
1200
1000
800
600
400
200
0
1987 1988 1989 1991 1992 1993 1994 1995 1996 1998 1999 2000 2001 2002 2003 2004
10
38
40
150
216
263
233
400
530
600
875
792
813
1000
1063
1665


ANALYSIS OF ADRs BY REPORTERS 2004
[n=1665]
Number of Reports
Year
1200
1000
800
600
400
200
0
1987 1988 1989 1990 1991 1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004
Government Doctors 10 32 36 39 87 129 198 191 303 419 489 480 608 573 496 651 646 988
Others (Pharmacist, Dentist) 0 3 2 1 12 6 2 9 27 40 62 61 141 74 118 162 169 352
GP/Private Specialist 0 1 2 4 51 81 68 33 70 61 51 44 65 38 94 49 60 83
Company 0 0 0 0 0 0 0 0 0 0 1 18 54 43 67 90 141 188
University 0 0 0 0 0 0 0 0 0 0 16 11 7 0 36 47 47 54

TOP TEN REPORTERS (DOCTORS) – 2004

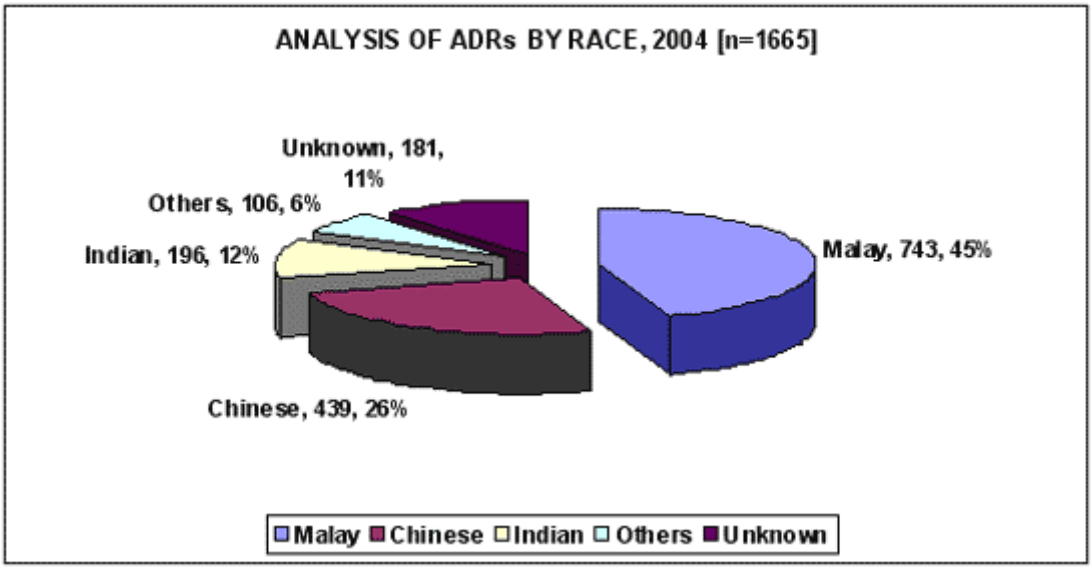
Name	Hospital / Institution	No. of Reports
Dr. Dawn Angela	Hosp. Kuala Lumpur	22
Dr. Ng Tin Guan	Hosp. Kuala Lumpur	22
Dr. Riza Hartini	Hosp. Selayang	18
Dr. Bavani Poobalan	Hosp. Selayang	17
Dr. Zainah Mokhtar	Hosp. Queen Elizabeth	11
Dr. Nik Raziha	Hosp. Tengku Ampuan Afzan	10
Dr. Gowri Sundram	Hosp. Kuala Lumpur	9
Dr. Essazul Imran	Hosp. Labuan	8
Dr. Chang San Kong		8
Dr. Qym Ho HK	Gleneagles Specialist Hosp.	8

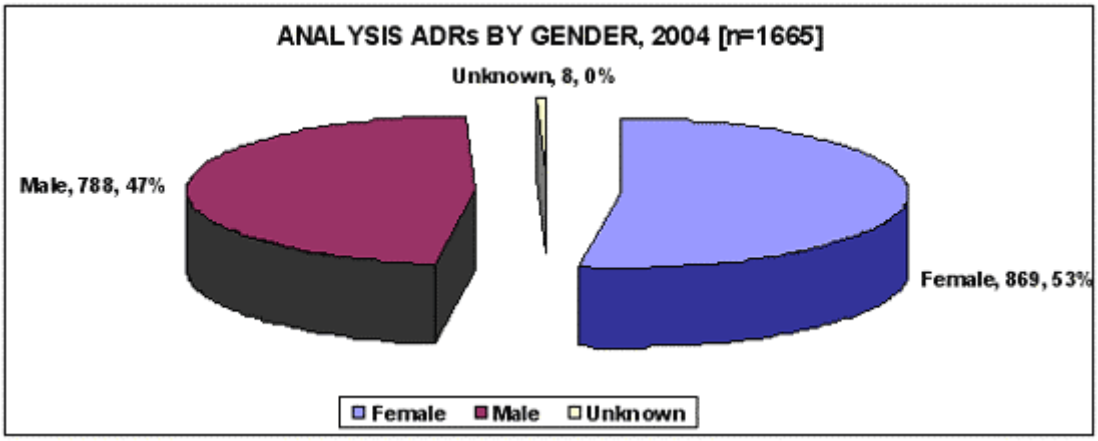
TOP TEN REPORTERS (PHARMACIST) – 2004

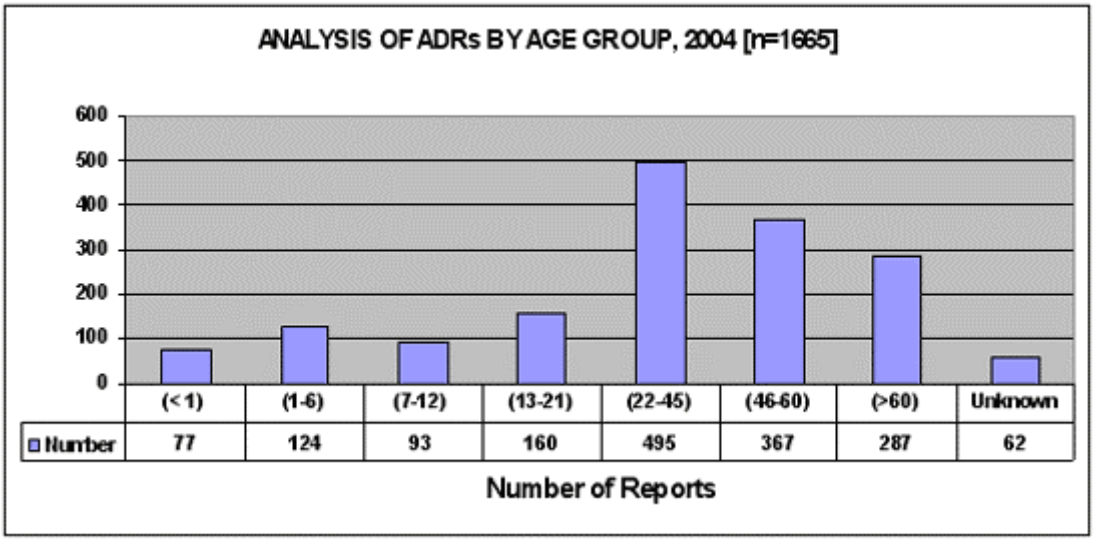
Name	Hospital / Institution	No. of Reports
Yoong Yuen sian	Hosp. Sultanah Aminah	22
Lau Chee Lan	Hosp. UKM	14
Shahnaz Bishahrin	Klinik Kesihatan Ampangan	12
Malathi Sri Raman	Klinik Kesihatan Bandar Baling	11
Pau Kiew Beng	UMMC	10
Shairyzah Ahmad Hisham	Hosp. UKM	6
Syarifah Jamaluddin	K.K. Kuala Terengganu	5
Salmi Abdul Razak	Poliklinik Komuniti Tanglin	4
Nurul Izzati	Hosp. Putrajaya	
Martina Hu Siew Meng	Hosp. Umum Sarawak	4

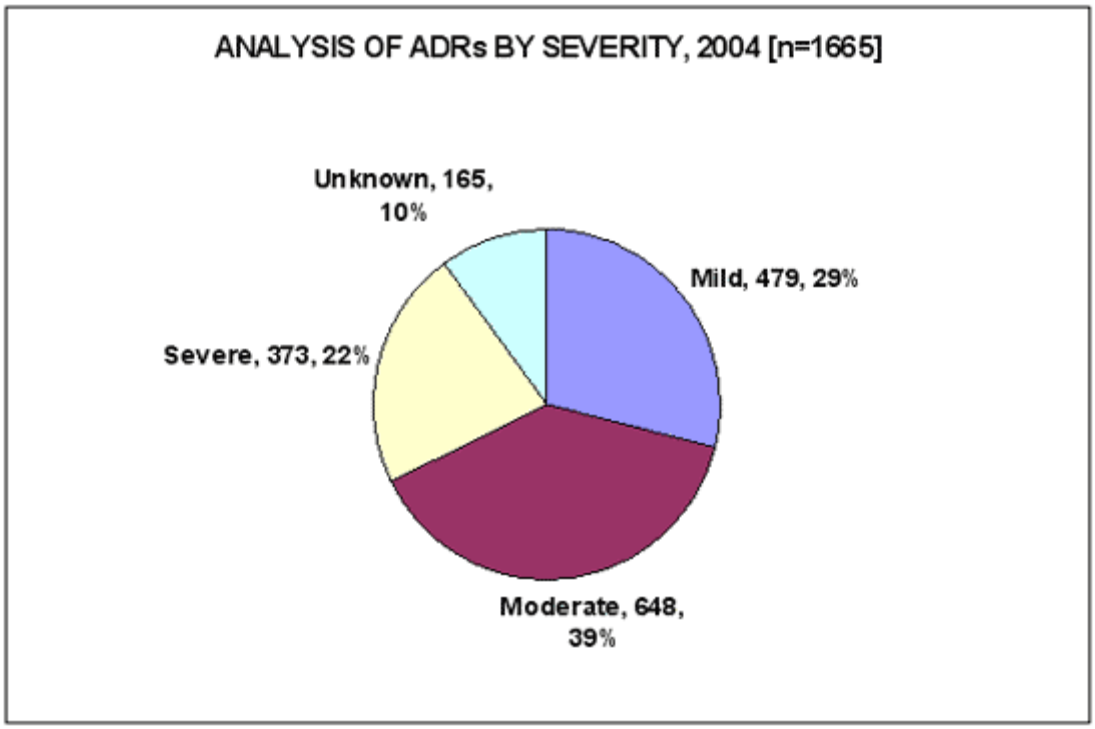
NUMBER OF REPORTS BY CATEGORY OF CAUSALITY, 2004 (1388)

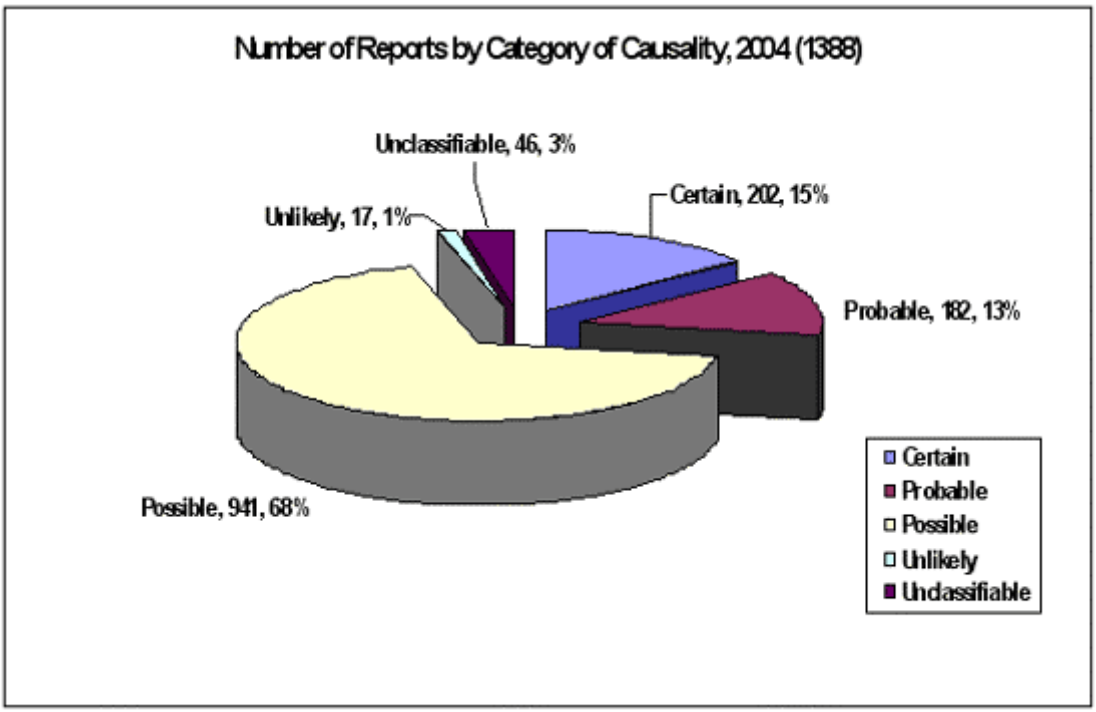
	N	%
Number of valid reports received	**1665**	**100**
Number of reports with causality assessed as:		
Certain	**202**	**12.1**
Probable	**182**	**10.9**
Possible	**941**	**56.5**
Unlikely	**17**	**1**
Unclassifiable	**46**	**2.8**


ANALYSIS OF ADRs BY RACE, 2004 [n=1665]
Unknown, 181, 11%
Others, 106, 6%
Indian, 196, 12%
Malay, 743, 45%
Chinese, 439, 26%
Malay
Chinese
Indian
Others
Unknown


ANALYSIS ADRs BY GENDER, 2004 [n=1665]
Unknown, 8, 0%
Male, 788, 47%
Female, 869, 53%
Female
Male
Unknown


ANALYSIS OF ADRs BY AGE GROUP, 2004 [n=1665]
600
500
400
300
200
100
0
(< 1)
(1-6)
(7-12)
(13-21)
(22-45)
(46-60)
(>60)
Unknown
Number
77
124
93
160
495
367
287
62
Number of Reports


ANALYSIS OF ADRs BY SEVERITY, 2004 [n=1665]
Unknown, 165, 10%
Mild, 479, 29%
Severe, 373, 22%
Moderate, 648, 39%


Number of Reports by Category of Causality, 2004 (1388)
Unclassifiable, 46, 3%
Certain, 202, 15%
Unlikely, 17, 1%
Probable, 182, 13%
Possible, 941, 68%
Certain
Probable
Possible
Unlikely
Unclassifiable