

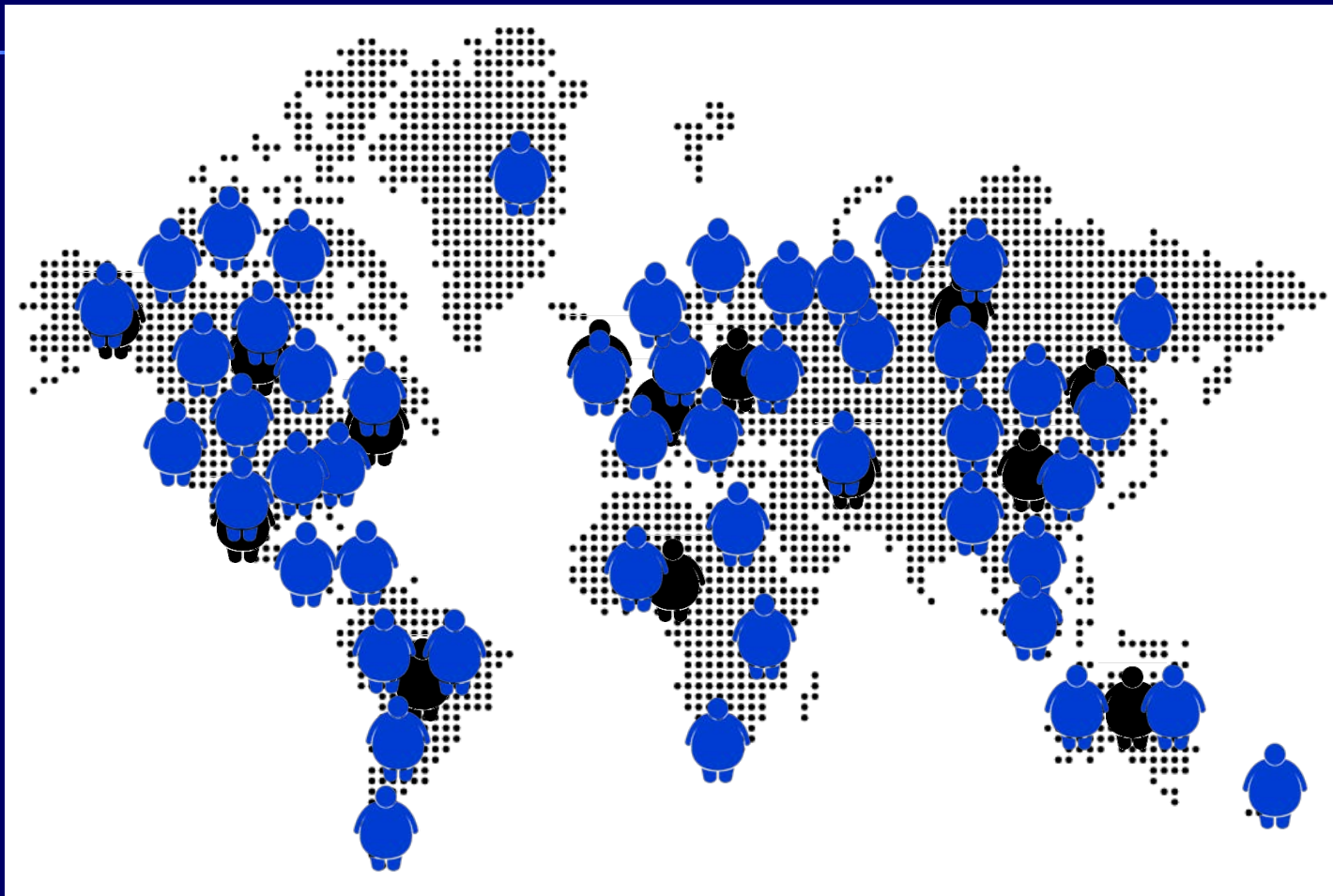


Illicit Slimming Agents: From the Notorious to the **UNBELIEVABLE**

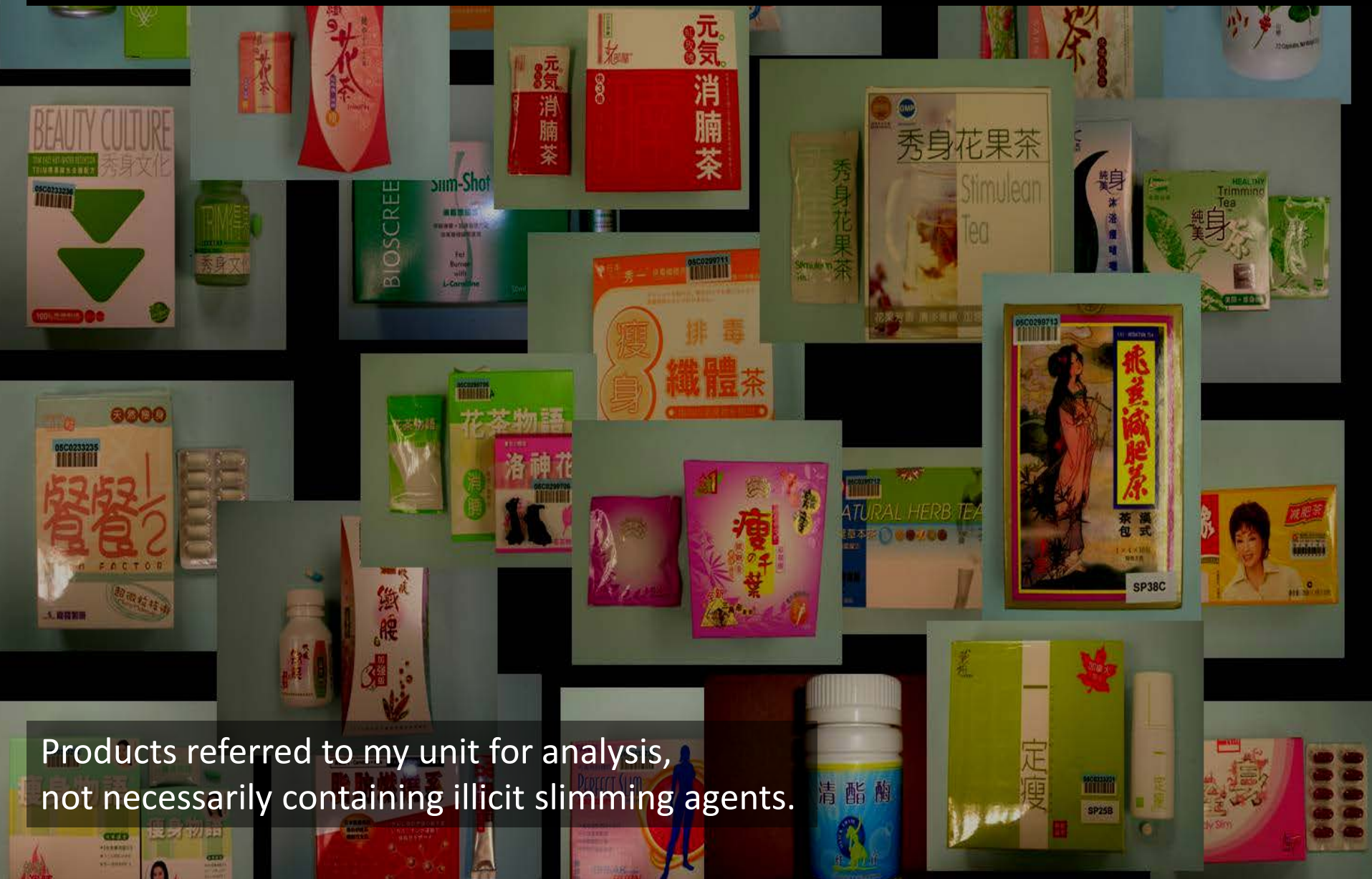
Dr Tony W L MAK

Consultant Pathologist, HA Toxicology Reference Laboratory
Chief of Service, Pathology, Princess Margaret Hospital

Obesity: 1980 / Now



Slimming Agents: Natural & Harmless



Products referred to my unit for analysis,
not necessarily containing illicit slimming agents.

Slimming Agents Toxicity



Depression and Suicide



Cardiac



Electrolyte disturbance

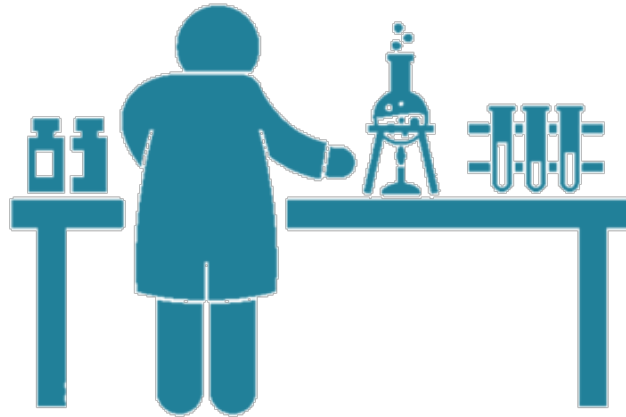


Endocrine disturbance



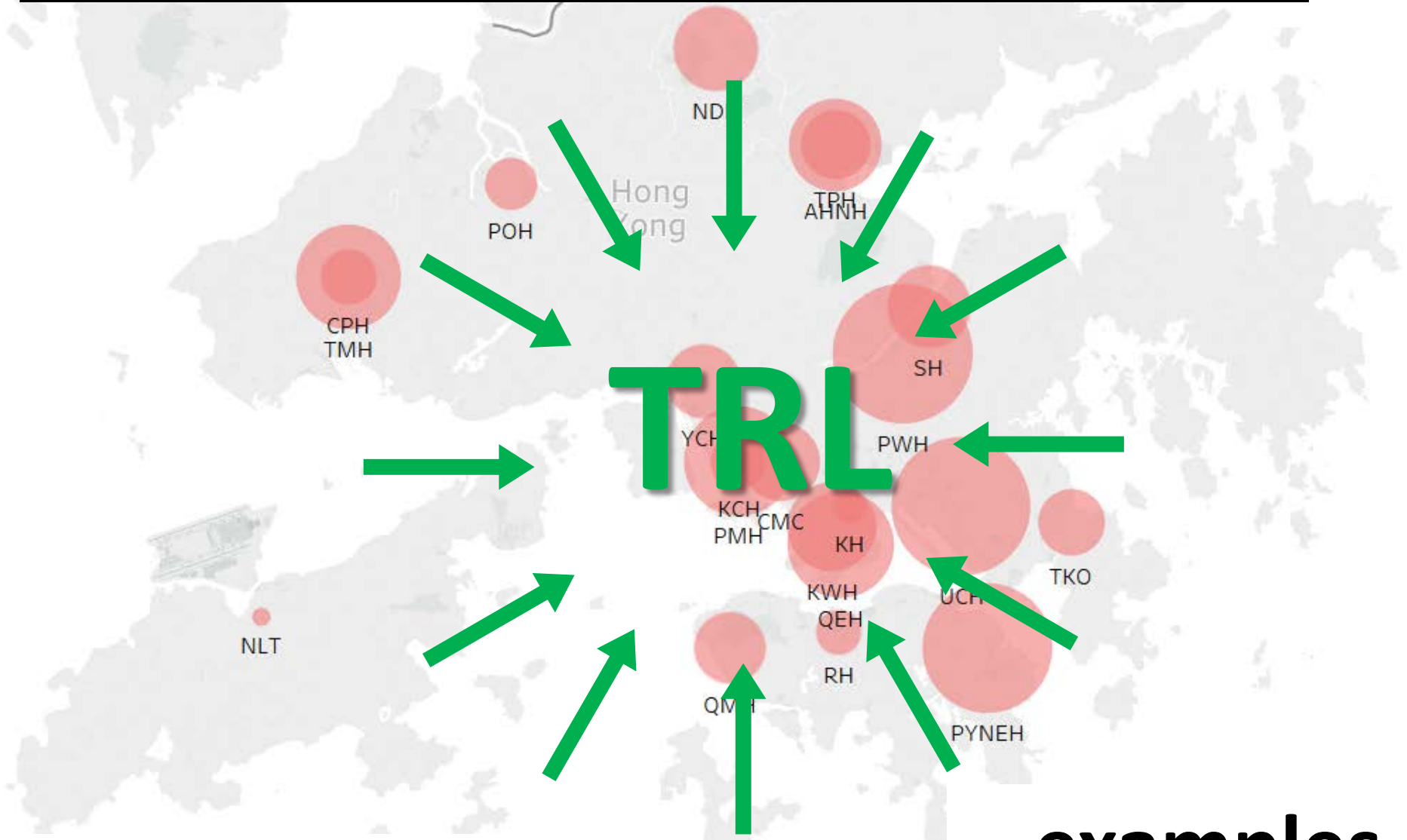
Psychosis

What causes the problem?



...requires laboratory investigation

Suspected slimming agent toxicity



TRL: Toxicology Reference Lab

...examples



Copyright © Informa UK, Ltd.
ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.3109/15563650.2010.517208

ARTICLE

Psychosis associated with sibutramine adulterated with sibutramine

Sibutramine Induces Psychosis?

Sibutramine



- Registered 1997
- Weight reduction:
 - Suppress appetite
 - Increase energy expenditure
- **Popular!**
- Severe cardiovascular side effect
- Banned in 2010



Side effects from Drug Insert

CVS	Tachycardia, palpitation, hypertension
GI	Constipation, nausea, hemorrhoid
Skin	S
Sensory	T
CNS	Dry mouth, insomnia, light-headedness, paraesthesia

No Psychosis !

Our observations

Intake stopped;
psychosis stopped



“Ingredients”:
魔芋，決明子，
螺旋藻，左旋肉
鹼，膳食纖維

Toxicology
Reference Lab

Sibutramine

Similar
Case



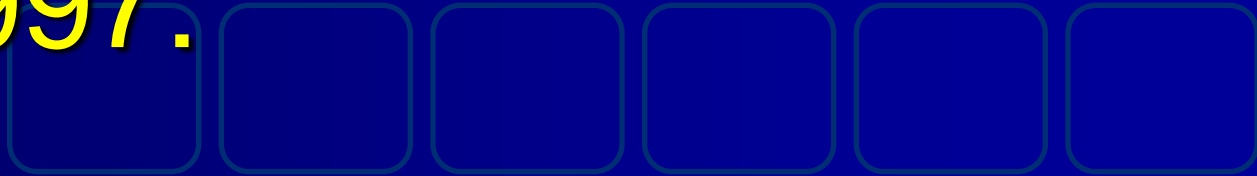
Delusion
Hallucination



Intake for
4 weeks



Sibutramine Use since 1997:



Psychosis documented?



World-wide, 8 cases in 13 years

Author	Country	Year	Case	Chief Presentation
Taflinski	Poland	2000	F/19	Hallucination
Cordeiro	Brazil	2002	M/20	Delusion
Mei	Holland	2004	F/36	Hallucination
Litvan	Spain	2007	F/40	Delusion
Fernandez	Spain	2007	M/50	Delusion
Lee	US	2008	F/26	Delusion
Dogangun	Turkey	2008	M/15	Hallucination
Gazdag	Hungary	2008	F/39	Delusion



- Retrospective review: 6 years
- Cases referred to TRL, who
 - took “herbal” slimming products
 - adulterated with sibutramine
 - presented with psychotic features



Products analyzed	92
-------------------	----

Adulterated with sibutramine	59
---------------------------------	----

Presented with psychosis	16
-----------------------------	----

Female:Male	15:1
-------------	------

Age	19 Years (15-47)
-----	---------------------

Drug history	4 weeks (1-12)
--------------	-------------------



Auditory hallucination	10
------------------------	----

Visual Hallucination	6
----------------------	---

Persecutory ideas	6
-------------------	---

Delusion	4
----------	---

Suicidal ideation	2
-------------------	---

Results



Population (Mil)

Hong Kong

7

The World

6875

Cases

16

8

Period (Yr)

6

13

Relative Incident >4000 : 1

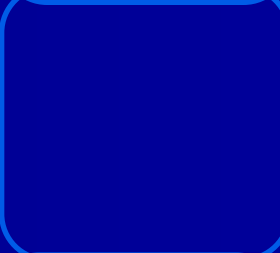


Discussion

- Psychosis uncommon world-wide but common in HK, why?
 - Sibutramine: **adulterated vs prescribed**
 - **Adulterated sibutramine:**
 - disguised as “herbal” / “natural” product
 - perceived as “safe”
 - liberal use: huge single/cumulative dose
- Elicited a dose-dependent side effect

Educate the public

東方日報 29/10/2010



Copyright © Informa UK, Ltd.
ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.3109/15563650.2010.517208

ARTICLE
Psychosis associat
adulterated with si

「天然成分」含禁藥 港病發率冠全球

亂食減肥品

唔死都失常

問題產品 亂服食減肥產品如同「玩命」！最近六年最少有七十三人因服食「天然成分」減肥藥，但獲准減肥西藥的產品後不獲入院個案。醫院管理局毒理參考化驗室追蹤分析○四年至去年的六十六宗服食減肥產品後入院個案，揭出一人死亡、一人因肝衰竭瀕臨換肝，十六人更因服食含減肥西藥西布曲明成分的減肥產品出現精神錯亂等驚人結果。「食到瘦」的比率更較全球同類個案發病率高出四千多倍。市民亂「嗲」減肥產品可能付上沉重代價，而毒理參考化驗室每揭發違規個案後即時通報衛生部門追查堵截。

接受治療時間最長超過五周。毒理參考化驗室顧問醫生李永權表示，受化驗及藥理追蹤的減肥產品雙稱「成分天然」，但證實含禁藥，甚至其他成分如動物甲狀腺組織。「呢啲(甲狀腺組織)係天然產品，但亂食就死人。」至於西布曲明是引致精神錯亂的字眼副作用，更因該類產品大行其道，令市民大量服食這類機械西藥成分的產品而令精神錯亂個案大加攀升。

▲沒有標示含西布曲明的「斯康歌」導致有市民服用後精神異常。

▲「玲瓏曲線」清腎減肥膠囊「含西布曲明量比註冊的減肥西藥高。」

▲「瘦身速」膠囊也沒有標示含西布曲明量比二十倍。

▲「瘦身速」膠囊也沒有標示含西布曲明量比二十倍。

藝人向減肥藥說「不」

楊靜
「減肥藥物有副作用，好耐以前都有發生！其實做帶氣運動都係好好嘅減肥方法，我就最鍾意游泳。最好多食蔬菜，總之減肥唔係嗲食喇。」

莊思敏
「我一直都唔主張內服食藥減肥，減肥方法可以去美容院做機，針對部位去啲，而平時我都會跑步，飲食方面會少油，少煎。」

Oriental Daily: slimming products cause psychosis



Clinical Toxicology (2010) **48**, 832–838
Copyright © Informa UK, Ltd.
ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.3109/15563650.2010.517208



informa
healthcare

ARTICLE

Psychosis associated with usage of herbal slimming products adulterated with sibutramine: a case series

SAMMY P.L. CHEN, MAGDALENE H.Y. TANG, SAU WAH NG, WING TAT POON, ALBERT Y.W. CHAN, and TONY W.L. MAK
Hospital Authority Toxicology Reference Laboratory, Princess Margaret Hospital, Hong Kong Special Administrative Region, China

Copyright © Informa UK, Ltd.
ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.3109/15563650.2010.517208

ARTICLE

Psychosis associat
adulterated with si

Fenfluramine

氟苯丙胺

Valvular Heart Disease and Pulmonary Hypertension

The New England Journal of Medicine

© Copyright, 1997, by the Massachusetts Medical Society

VOLUME 337

August 8, 1997

NUMBER 9

VALVULAR HEART DISEASE ASSOCIATED WITH FENFLURAMINE-
PHENTERMINE

JOHN M. COLLINS, M.D., JACK L. HANCOCK, M.D., MICHAEL D. MCGOON, M.D., DONALD D. HENSRUD, M.D., M.P.H.,
ROBERT M. GIBSON, M.D., WILLIAM D. EDWARDS, M.D., AND HARTZELL V. SCHAFF, M.D.

Banned!

- 2002
- F/17
- Bought 七仙七日常駐青免疫膠囊
- From Shenzhen
- Claimed: purely herbal
- Took the capsules for 2 months
 - Chest discomfort
 - Shortness of breath
 - Echocardiography: MR and AR





claims to be purely herbal



Fenfluramine detected!

HK J Paediatr (new series) 2005;10:55-58

Case Reports

Valvular Heart Disease Caused By Chinese Proprietary
Slimming Medicine Adulterated With Fenfluramine

K CHANG, TWL MAK, L KWONG, KT SO

Discussion:

Banned drugs

→ Banned from the legal market only!

Jianmeisu (健美素)

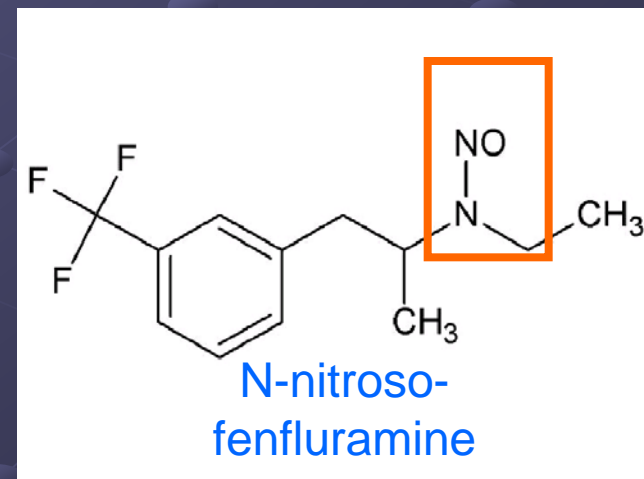
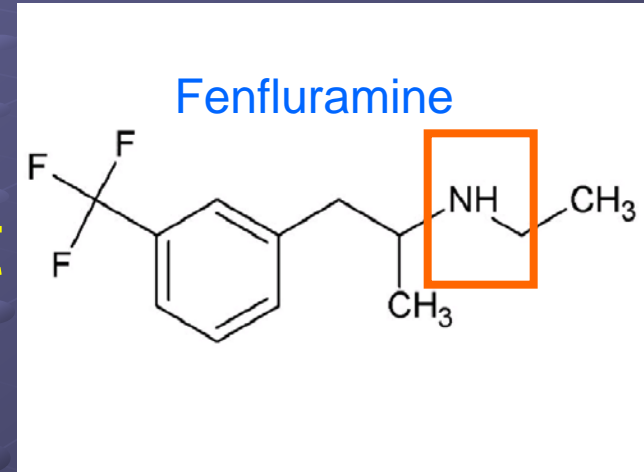
- ◆ 2004
- ◆ F/33
- ◆ Weight reduction
- ◆ Took Jianmeisu x 6 weeks
- ◆ Sold >100 boxes/month in HK
- ◆ Claimed: 12 benign herbs

Jianmeisu (健美素)

- ◆ Fulminant hepatic failure!
- ◆ Saved by liver transplantation
- ◆ Cause of liver failure??
- ◆ Idiosyncratic reaction to a herb?
- ◆ TRL found **N-nitroso-fenfluramine (NNF)**
- ◆ **NNF** – an analogue of fenfluramine
- ◆ Department of Health:
→ banned the product

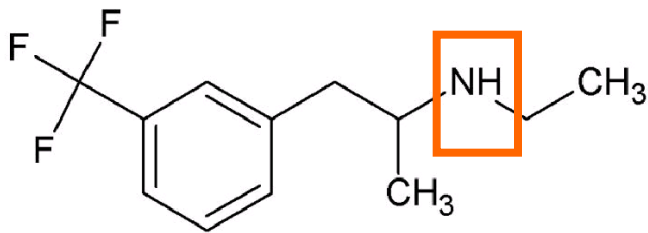
Jianmeisu (健美素)

- ◆ Fenfluramine
- ◆ Banned slimming agent
- ◆ **NNF** – an analogue
- ◆ Singapore, UK
- ◆ Japan >800 cases



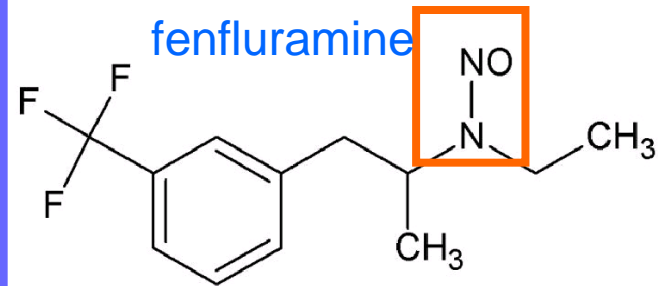
Jianmeisu (健美素)

Fenfluramine



Heart valve defects
Pulmonary HT
No liver toxicity
Appetite suppressant

N-nitroso-fenfluramine



??
??
Liver toxicity ++++
Appetite suppressant x

Jianmeisu (健美素)

04C0309660

N-nitroso-fenfluramine

沖劑藥丸竟達數十種

少女濫服保健品換肝保命



醫院每月都收到一至兩宗服用中成藥導致肝至肝衰竭的個案。

近年市面中成藥保健食品



呈報衛生署 中藥不良反應個案

(2000年至2004年6月)

數目：40宗證實個案(另22宗懷疑)
人數：49人(20男、29女)
年齡：6-87歲
入院人數：38人(6人需深切治療)
個案類別：34宗服用中草藥、
6宗服用中成藥

資料來源：衛生署

中藥中毒案 今年大幅飆升

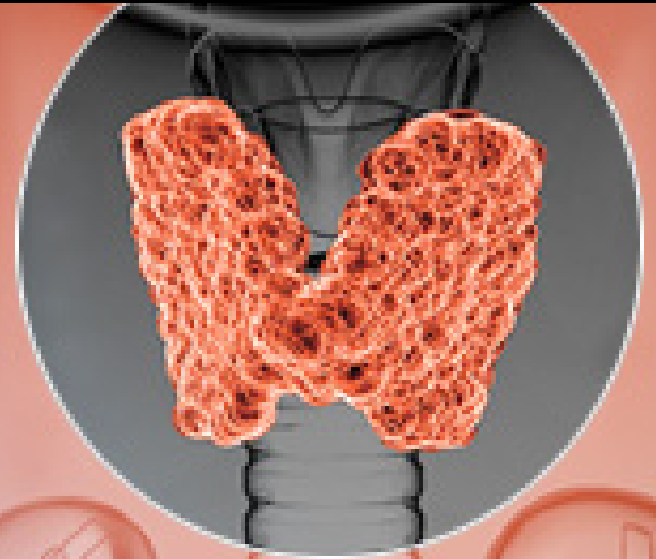
衛生署由二〇〇〇年至今年六月期
共接獲六十二宗懷疑中藥不良反應的呈
案，當中大部分在今年發生。截至本月

Jianmeisu (健美素)

- ◆ Never registered drug
- ◆ Used in illicit products
- ◆ No clinical testing of safety!

Thyrotoxicosis

- Excessive sweating
- Heat intolerance
- Increased bowel movements
- Tremor (usually fine shaking)
- Nervousness; agitation
- Rapid heart rate
- Weight loss
- Fatigue
- Decreased concentration
- Irregular and scant menstrual flow



Food consumption

Body weight

Thyroid Hormone: Obesity Rx

- Thyroxine - 19th century
- Side effects!
- 1978: FDA against such use
- Go away?
- Still being reported everywhere! UK, USA, Japan...

- Must present in Hong Kong!
→ Several analytical attempt: no thyroxine

Thyroid Hormone: Obesity Rx

- July 05, M/41, good past health
- Severe muscle weakness + Hypokalaemia
- → Hypokalemic periodic paralysis
- Thyroid function test:
 - TSH: undetectable
 - FT4: high
- → Thyrotoxic periodic paralysis
- Taking slimming pills (“Caltrate”) for how long?

Thyroid Hormone: Obesity Rx

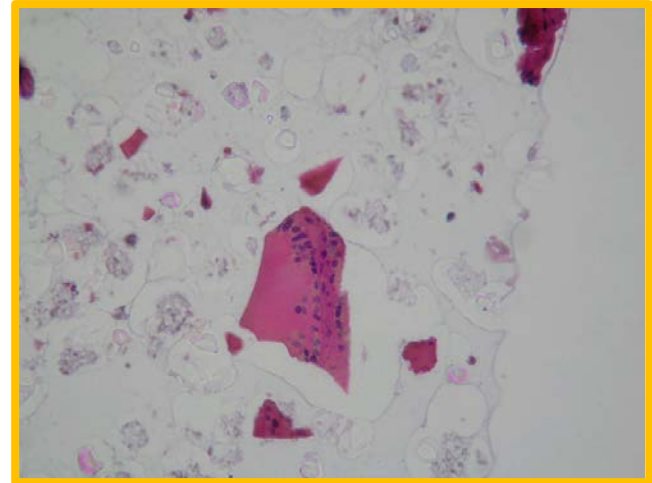
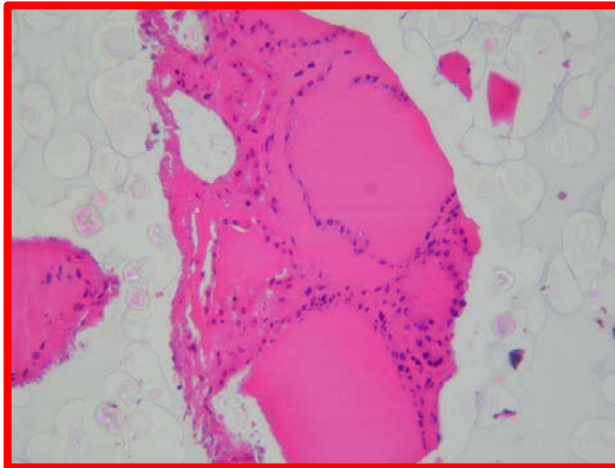
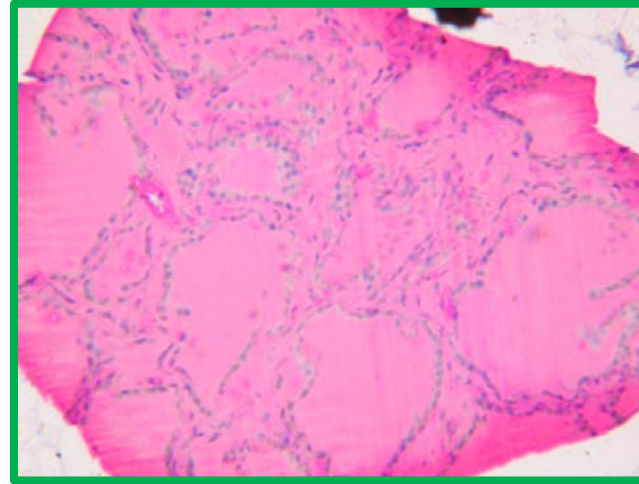
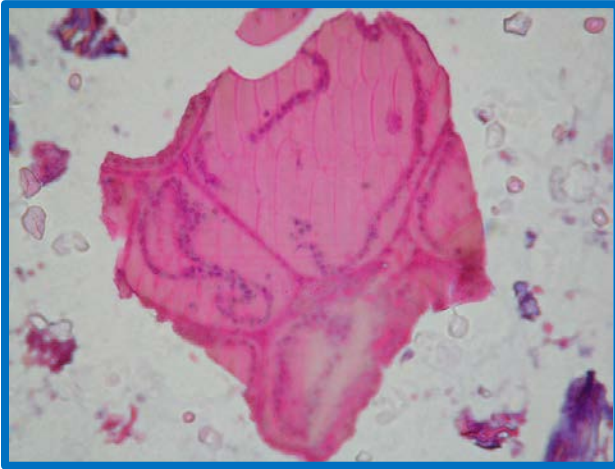
- Slimming pill content for microscopy:



**NOT thyroxine but
thyroid tissue!**

Thyroid Hormone: Obesity Rx

→ Animal thyroid tissue:



Conclusion

- Thyroid hormone is used locally as slimming agent
- Animal thyroid tissue is the most common form

Clinical Toxicology (2008) 46, 290–292
Copyright © Informa Healthcare USA, Inc.
ISSN: 1556-3650 print / 1556-9519 online
DOI: 10.1080/15563650701381179

ARTICLE

Factitious thyrotoxicosis and herbal dietary supplement
for weight reduction

W.T. POON, S.W. NG, C.K. LAI, Y.W. CHAN, and W.L. MAK

Toxicology Reference Laboratory, Princess Margaret Hospital, Hong Kong, Hong Kong

Desoxy-D2PM

Desoxy-D2PM = 2-Diphenylmethylpyrrolidine

What is “Desoxy-D2PM”?



Appetite suppression



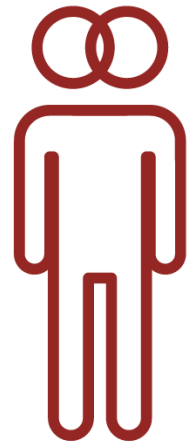
neuroregulatory

**More than a slimming agent
It is an “emerging” drug of abuse!**

arrhythmia

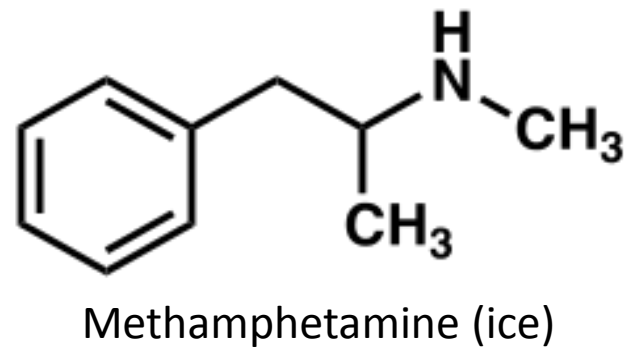
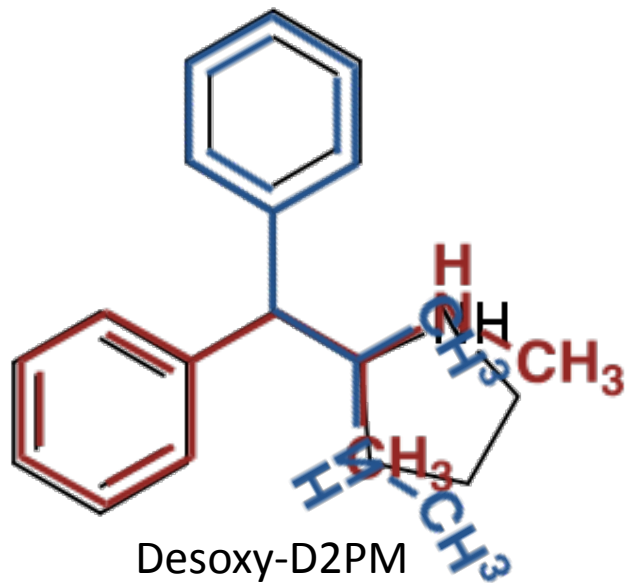


Violent behavior



Psychosis

Chemical structure



Two cases in July 2016

- Slimming pills bought from Thailand
 - Admitted for hallucination
 - Contents claimed to be all natural
 - Analysis showed desoxy-D2PM
-
- Another case of suicidal attempt with drug overdose
 - Urine analysis showed desoxy-D2PM



Recall



Recall by the Department of Health

Discussion

- Drugs of abuse
- Available to the public in convenience stores!

Desoxy-D2PM: a novel psychoactive substance in convenience stores

Hong Kong Med J 2016;22:515

DOI: 10.12809/hkmj166018

To the Editor—Novel psychoactive substances (NPSs) are recently available unlicensed drugs that are chemically or pharmacologically similar to conventional drugs of abuse. Their rapid and protean emergence has created many challenges for clinicians, laboratories, social workers, and regulatory authorities. Our laboratory has repeatedly identified NPSs.^{1,2} We report the discovery of 2-(diphenylmethyl)-pyrrolidine (desoxy-D2PM),

unintentional use by the general public. This case and our previous local reports of NPS^{1,2,5} highlight the importance of a toxicology surveillance system in Hong Kong.

Nike KC Lau, MB, ChB, MA

YK Chong, MB, BS, FHKCPath

Magdalene HY Tang, PhD

CK Ching, FRCPA, FHKAM (Pathology)

Tony WL Mak *, FRCPath, FHKAM (Pathology)

Slimming agents:
A 5-year review of TRL findings

Overview of cases

43 cases

Severity:

1	fatal	(pulmonary HT, aortic regurgitation, right heart failure)
4	severe	(acute renal failure; liver failure; myocardial infarction; severe tachycardia)
18	moderate	
20	minor	

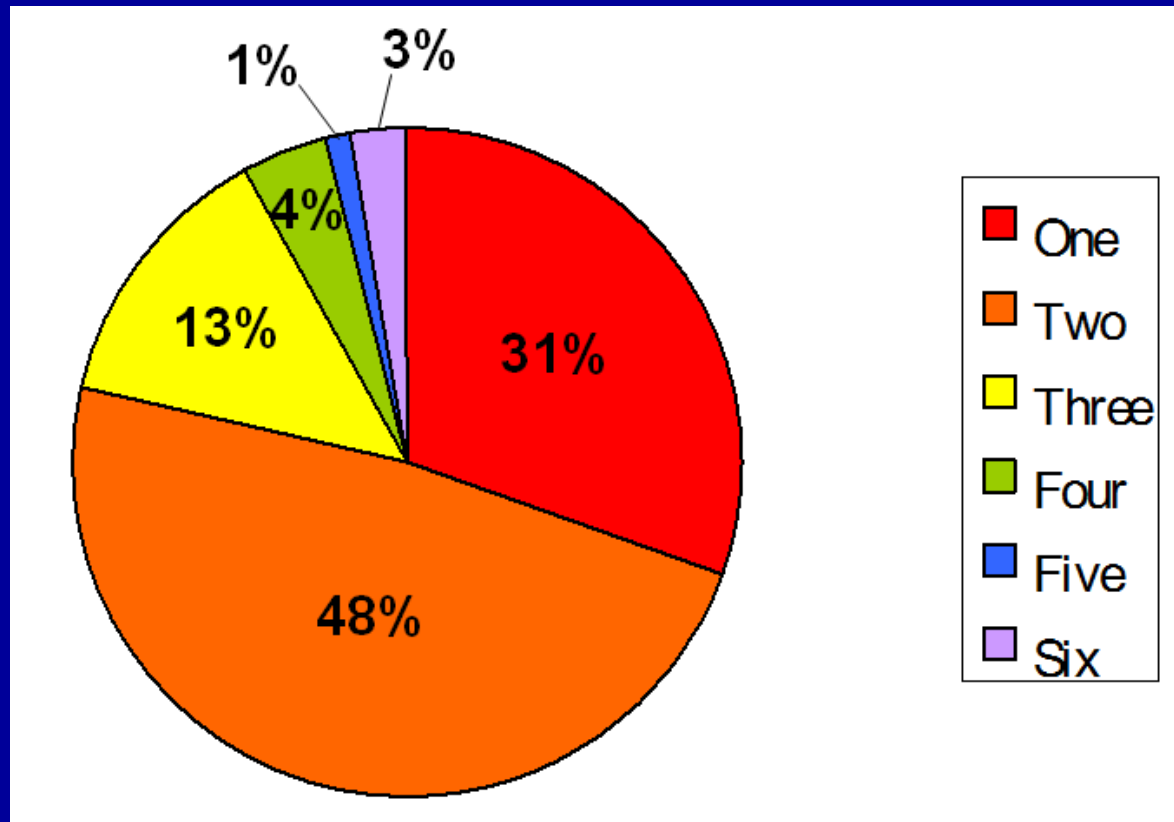
Overview of illicit agents

Illicit practice or means	Illicit agent
Adulteration	Sibutramine
Analogue	N-desmethyl-sibutramine N-bisdesmethyl-sibutramine N-nitrosofenfluramine
Banned drug	Fenfluramine Phenolphthalein
Inappropriate indication	Anthraquinone Bisacodyl Hydrochlorothiazide Spironolactone
Thyroid hormone	Animal thyroid tissue Tiratricol Thyroxine

... it gets even worse...

Not just a single agent....

.... but **2**, **3**, **4**, **5** and even **6** agents added together



Source

- Overseas
- Local slimming centres / beauty shops
- General practitioners (tiratricol, thyroxine)
- @ *INTERNET*



What can we do?

Drug regulatory bodies

Surveillance
Legislation

Laboratory staff

Active method development

Medical staff

Awareness
History taking

General public

Education

BJCP British Journal of Clinical
Pharmacology

Case reports on a diversity of
weight-reducing
agents: from the well known
to the unexpected

Magdalene H. Y. Tang, Sammy P. L. Chen, Sau W. Ng,
Albert Y. W. Chan & Tony W. L. Mak

*Hospital Authority Toxicology Reference Laboratory, Block P, Princess Margaret Hospital, Laichikok,
Hong Kong, China*

Best Journal Article Award

Thank you!