Do You Know What You're Snorting?

(Cocaine Cutting Agents – A Discussion)

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*Dyna**LIFE**Dx*

Edmonton, Alberta

Roundtable Session R305

IATDMCT 2009, Montreal

INTRODUCTION

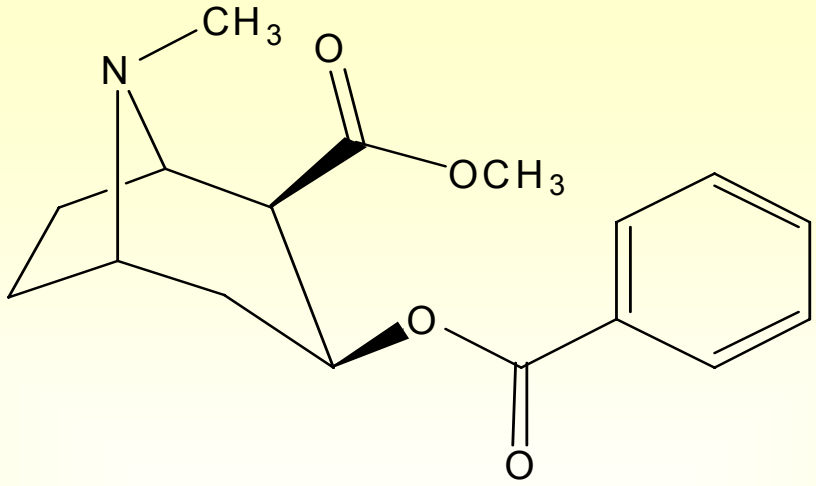
- Cutting agents are substances deliberately added to illicit drugs at some stage of production, packaging or distribution.
- Rationale for adding such agents include:

1. Provide a similar or complimentary effect with a cheaper compound (e.g. procaine, lidocaine, benzocaine).
2. Attenuate side effects (e.g. diltiazem, hydroxyzine)
3. Extend the supply of illicit drug, thus increasing profits (e.g. salt, lactose, baking soda)

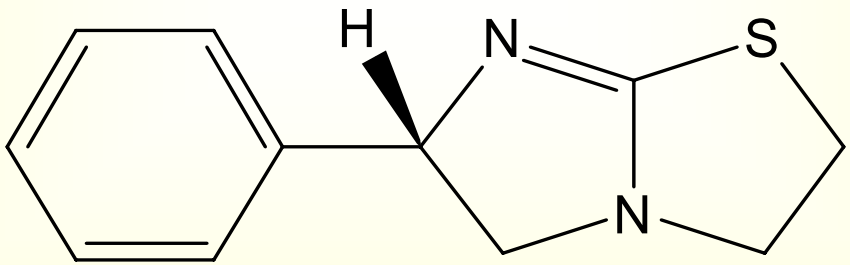
Something Strange!

November, 2005

Levamisole detected in urine extracts containing cocaine and its metabolites.



Chemical Structure of Cocaine



Chemical Structure of Levamisole

LEVAMISOLE

- Active l-isomer of tetramisole
- Discovered in 1966, Janssen Pharmaceutica, Belgium
- Original indication: antibiotic
- Eventual uses:

  - Anthelmintic in veterinary applications

    e.g. - BIG T Hog Dewormer Pellets 800 mg/Kg (Feed-Rite): 25 kg bags
    - Break-Away Hog Wormer Pellets
    - CO-OP Sow and Pig Wormer

  - Chemotherapeutic adjuvant to fluorouracil in colon cancer

    Mechanism of action:
    - Immunomodulator
      - potentiates action of interferon and interleukin-2
      - restores hypofunctional T-lymphocytes and phagocytes to normal.

- Discontinued for human use in Canada, August, 2005

  - questionable toxicity, lack of clinical efficacy

- Health Canada Drug Product Database

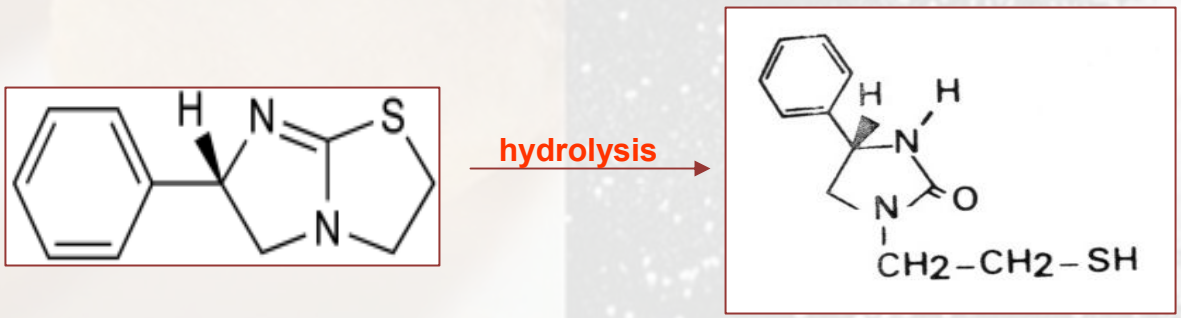
  - 37 discontinued products

Levamisole Pharmacokinetics

Absorption: rapid, t_{max} ~ 1 to 2h.

Metabolism: ~97% (t½: 5.6h)

- OMPI (phenylimidazolide)
  - ► active (levamisole a pro-drug?)



- para-hydroxylation
- glucuronidation

LEVAMISOLE TOXICITY

- **Hematologic – agranulocytosis** (0.4 - 20%)
- Hepatic – increased ALT and bilirubin
- Renal – proteinuria
- Respiratory – dyspnea
- Gastrointestinal – diarrhea (~13%)
- Dermatologic – dermatitis (5 – 7%)
- Neurologic – fatigue, weakness (8%); seizures (rare)
- Psychiatric – irritability, anxiety, psychosis

Febrile Neutropenia

- Neutropenia: neutrophil < 1
- Agranulocytosis: neutrophil < 0.1
- Febrile Neutropenia:
  - Temp > 38°C + neutrophil < 1
  - Likely underlying severe infection
  - High mortality rate (2.5-20%)

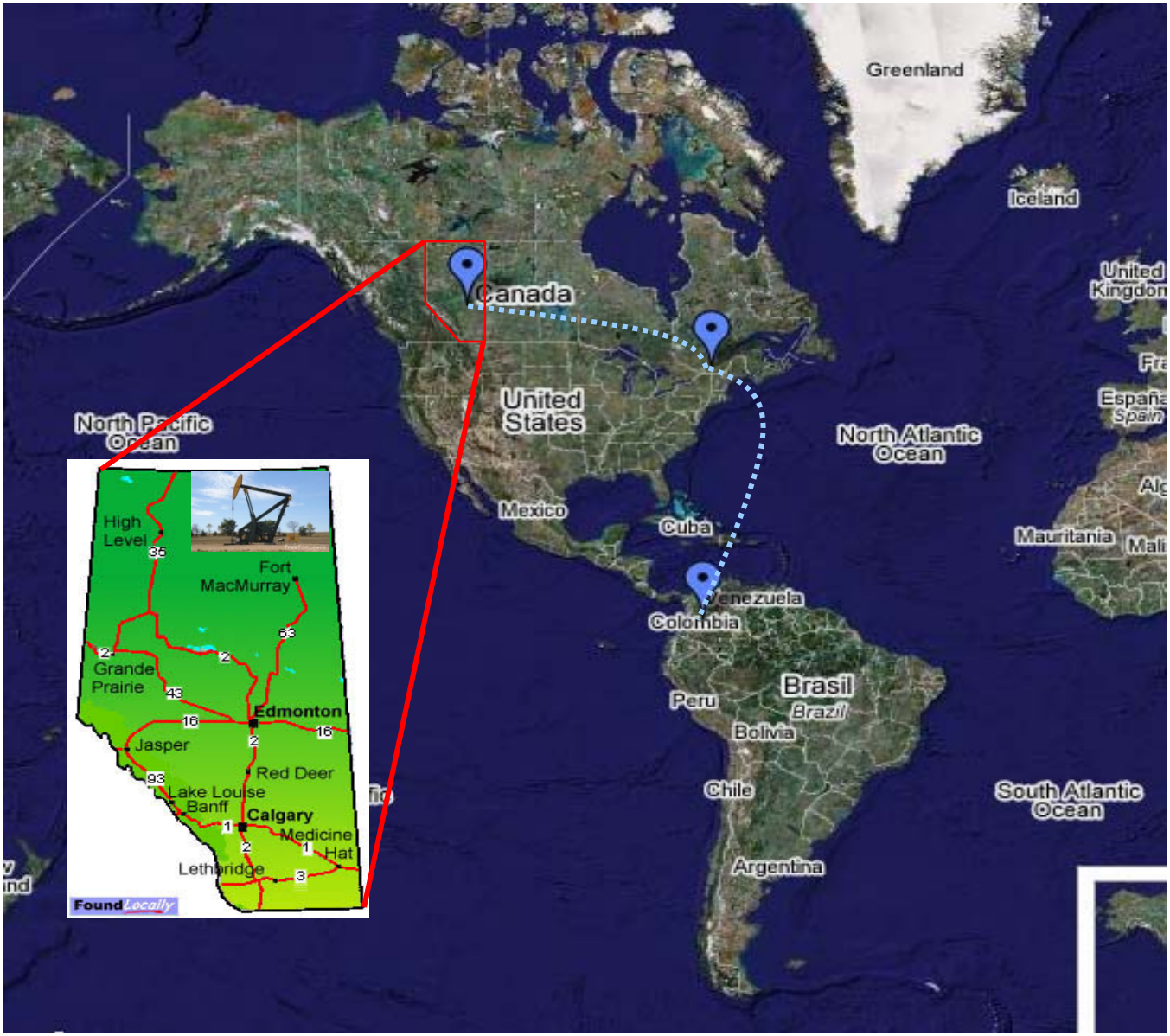
Proposed Mechanism of Action

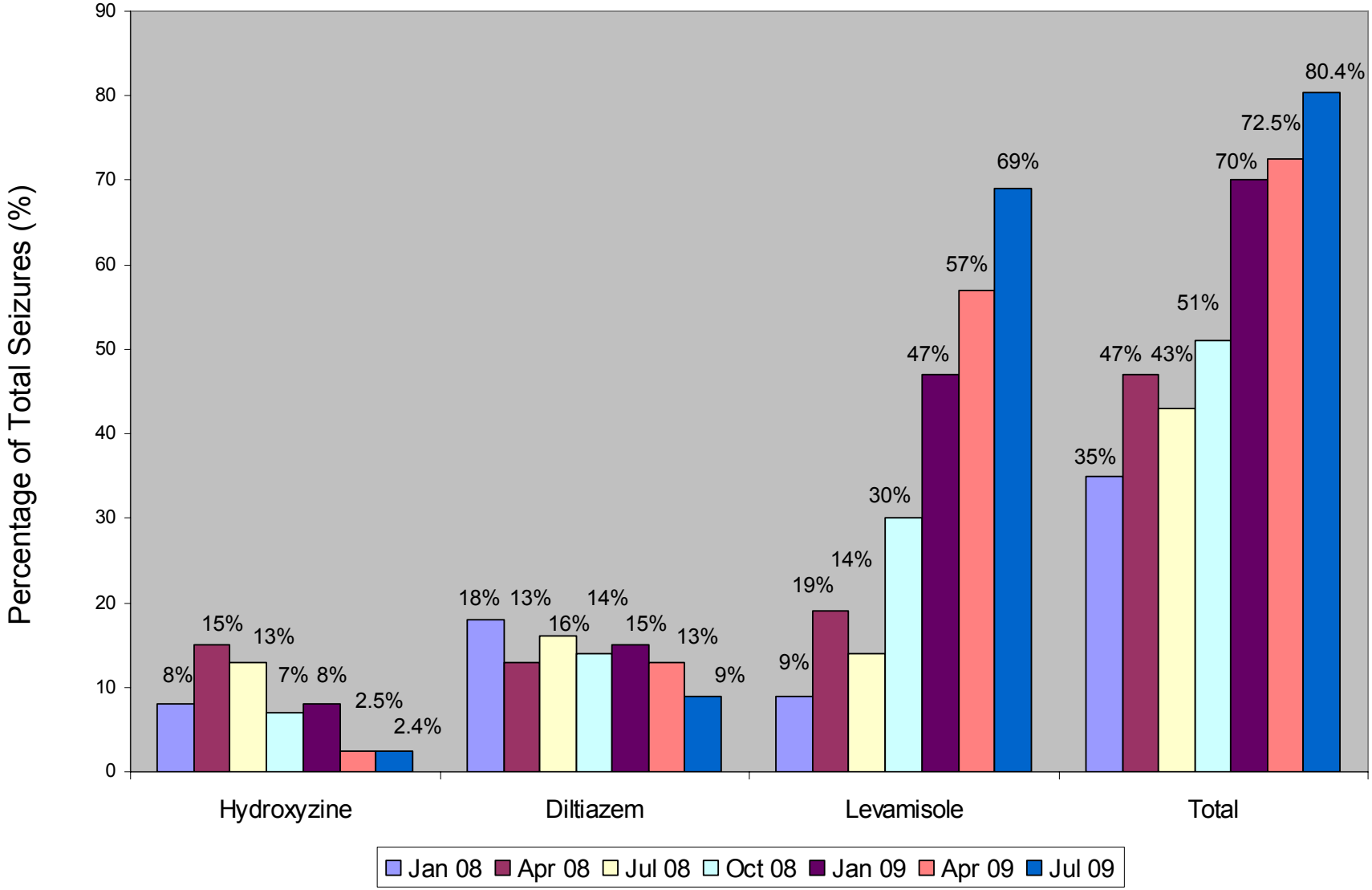
- Immune complex deposition on neutrophils → complement activation → cell lysis
- Anti-granulocytic antibodies
- Bone marrow suppression

Blood. 1980;56:388-396.

MAJOR DRUG SMUGGLING ROUTES THROUGH NORTH AMERICA

1) **Drug Situation in Canada, 2006. http://www.rcmp-grc.gc.ca/drugs/drugs_2006_e.html**
2) **Canada and the Transcontinental Drug Links**Stratfor Articles, October 15, 2007. http://www.stratfor.com/analysis/canada_and_transcontinental_drug_links

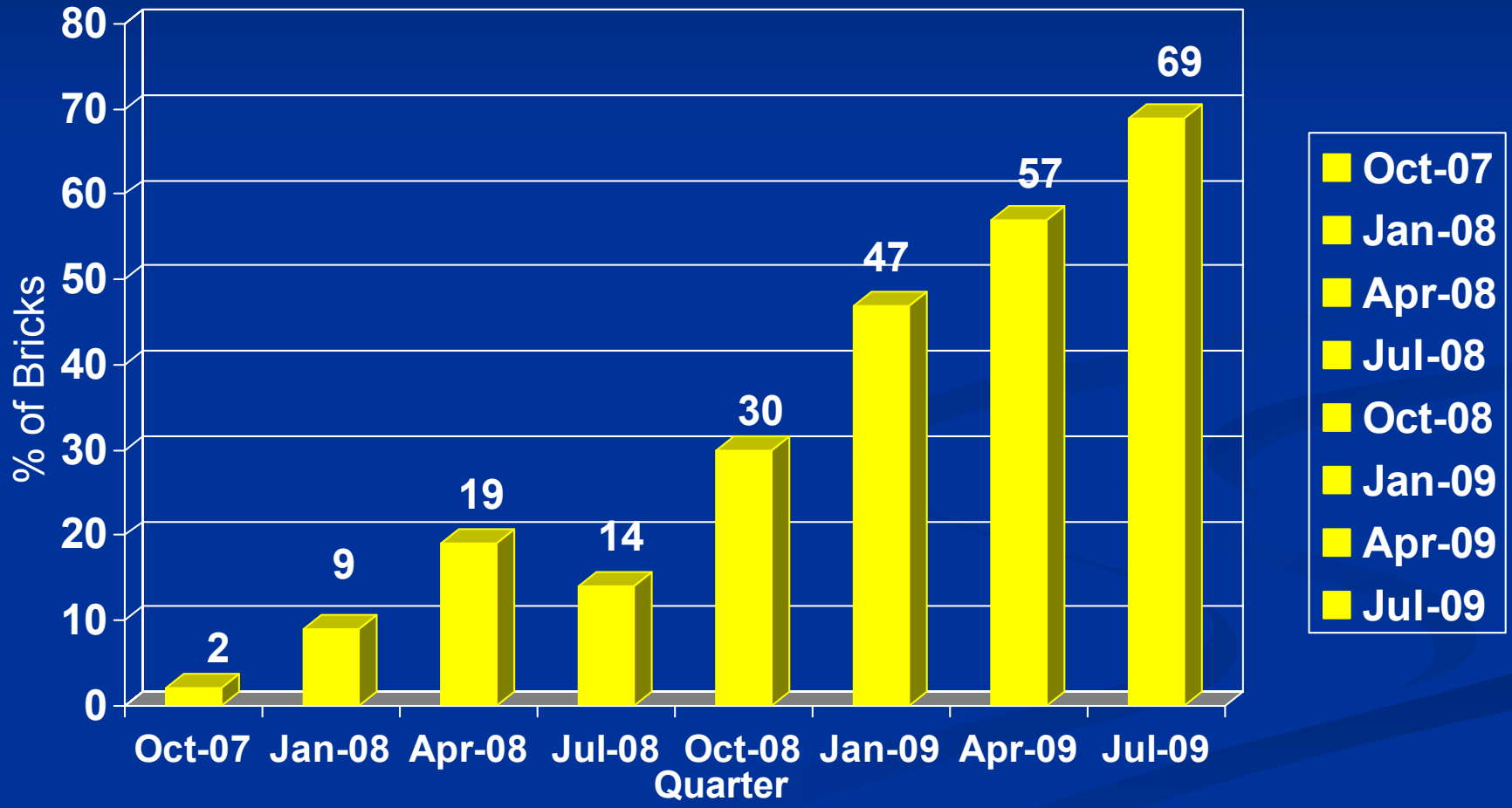

Greenland
Iceland
United Kingdom
Canada
United States
North Pacific Ocean
North Atlantic Ocean
España
Spain
Mexico
Cuba
Mauritania
Venezuela
Colombia
Brasil
Brazil
Peru
Bolivia
Chile
Argentina
South Atlantic Ocean
High Level
Fort MacMurray
Grande Prairie
Edmonton
Jasper
Red Deer
Lake Louise
Banff
Calgary
Medicine Hat
Lethbridge
FoundLocally



Prevalence of three major pharmaceutical cutting agents in seized U.S. cocaine exhibits

(personal communication from Dr. J. Casale, Drug Enforcement Administration, U.S. Department of Justice)

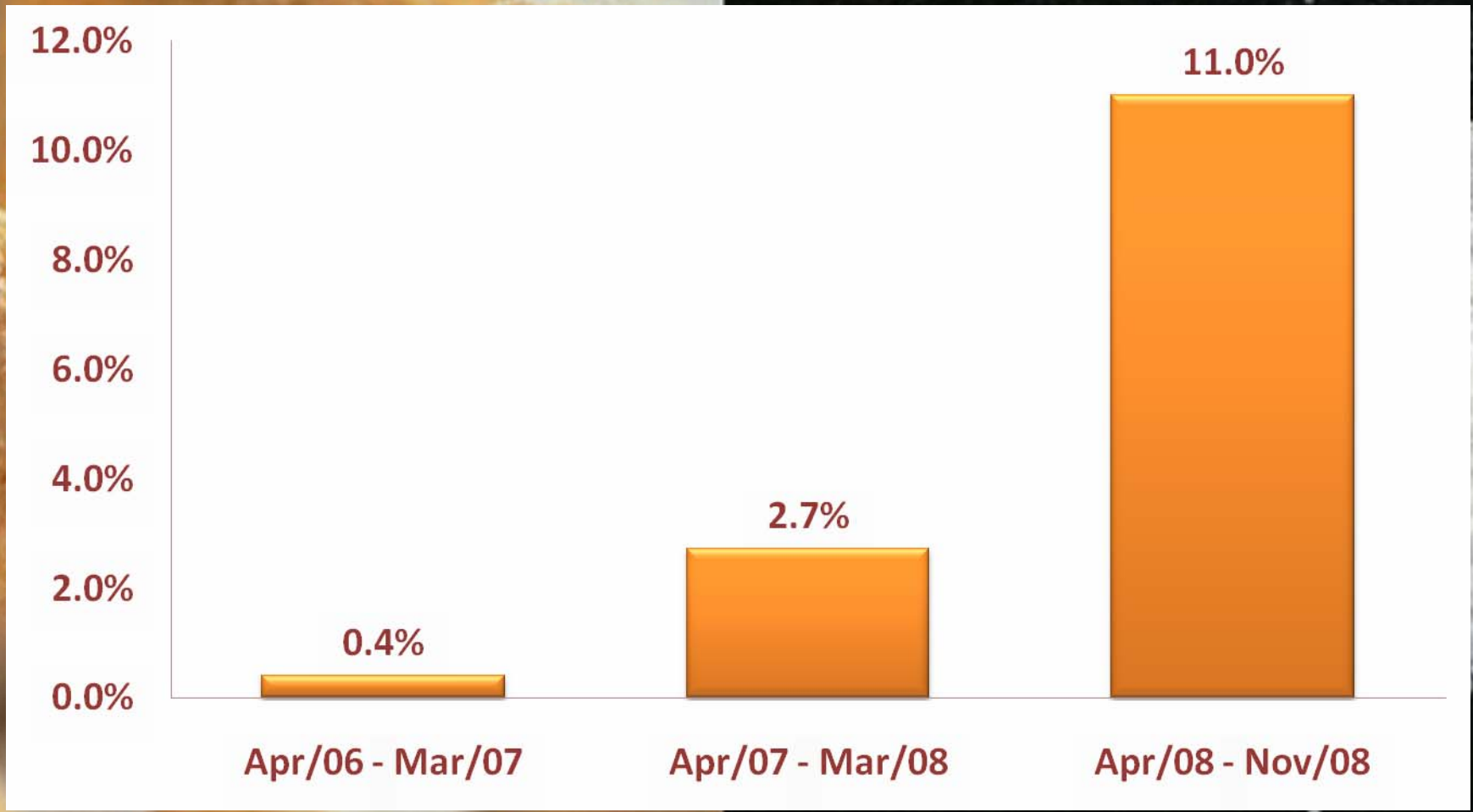
Percentage of Cocaine Bricks Containing Levamisole (U.S. Domestic Seizures)*



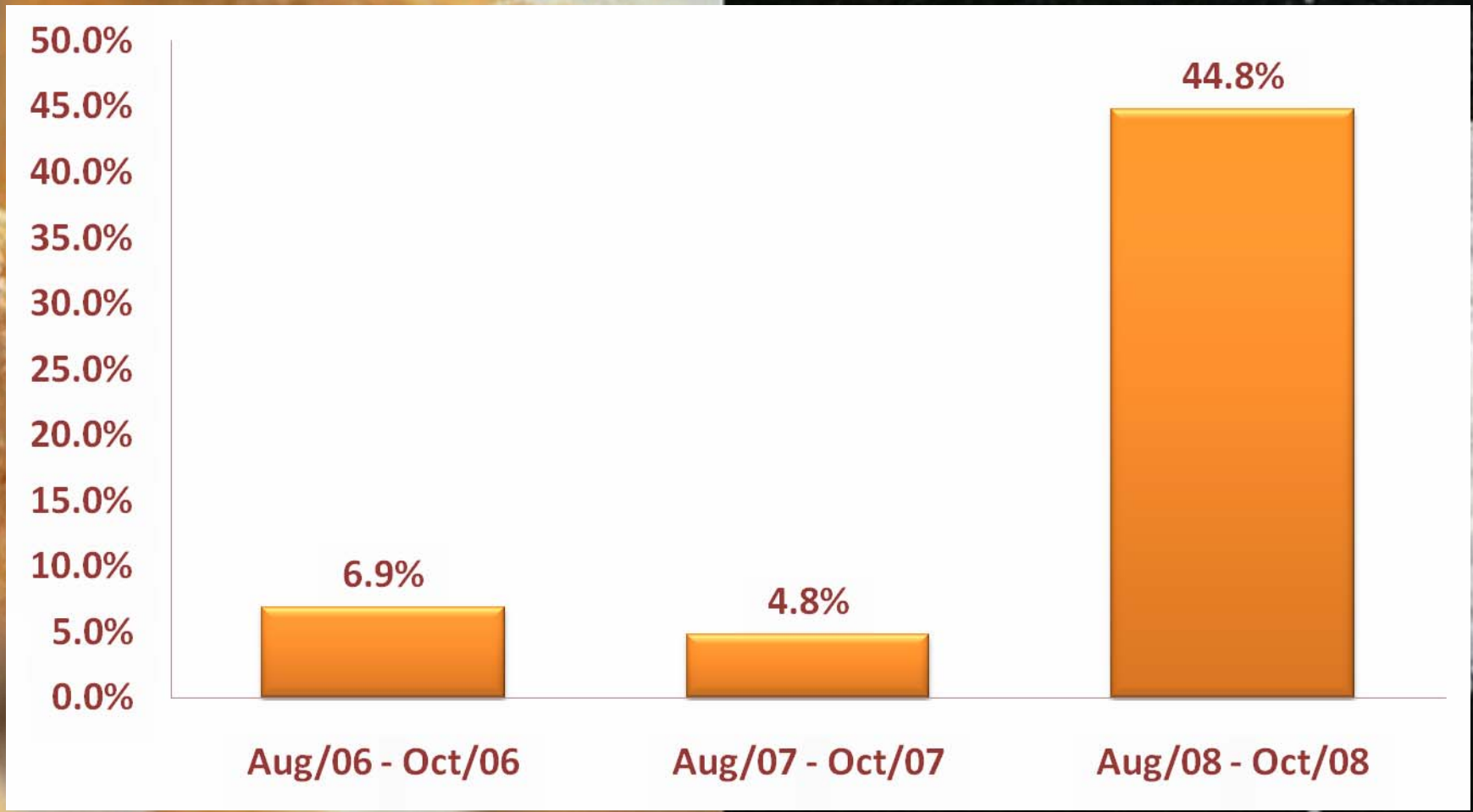
** Personal Communication, Dr. John Casale, U.S. Drug Enforcement Administration*

Royal Canadian Mounted Police

Levamisole Adulterated Cocaine in Alberta



Cocaine/Levamisole Detection at UAH



Toxicology Testing for Levamisole

Cocaine Metabolite Immunoassay

(If positive or reading >20% above drug free specimen)

Gas chromatography/Mass Spectrometry

(GC/MS)

Toxicology Testing for Levamisole GC/MS

Urine Specimen (2 mL)

Extraction

Injection into GC/MS

Toxicology Testing for Levamisole GC/MS (cont.)

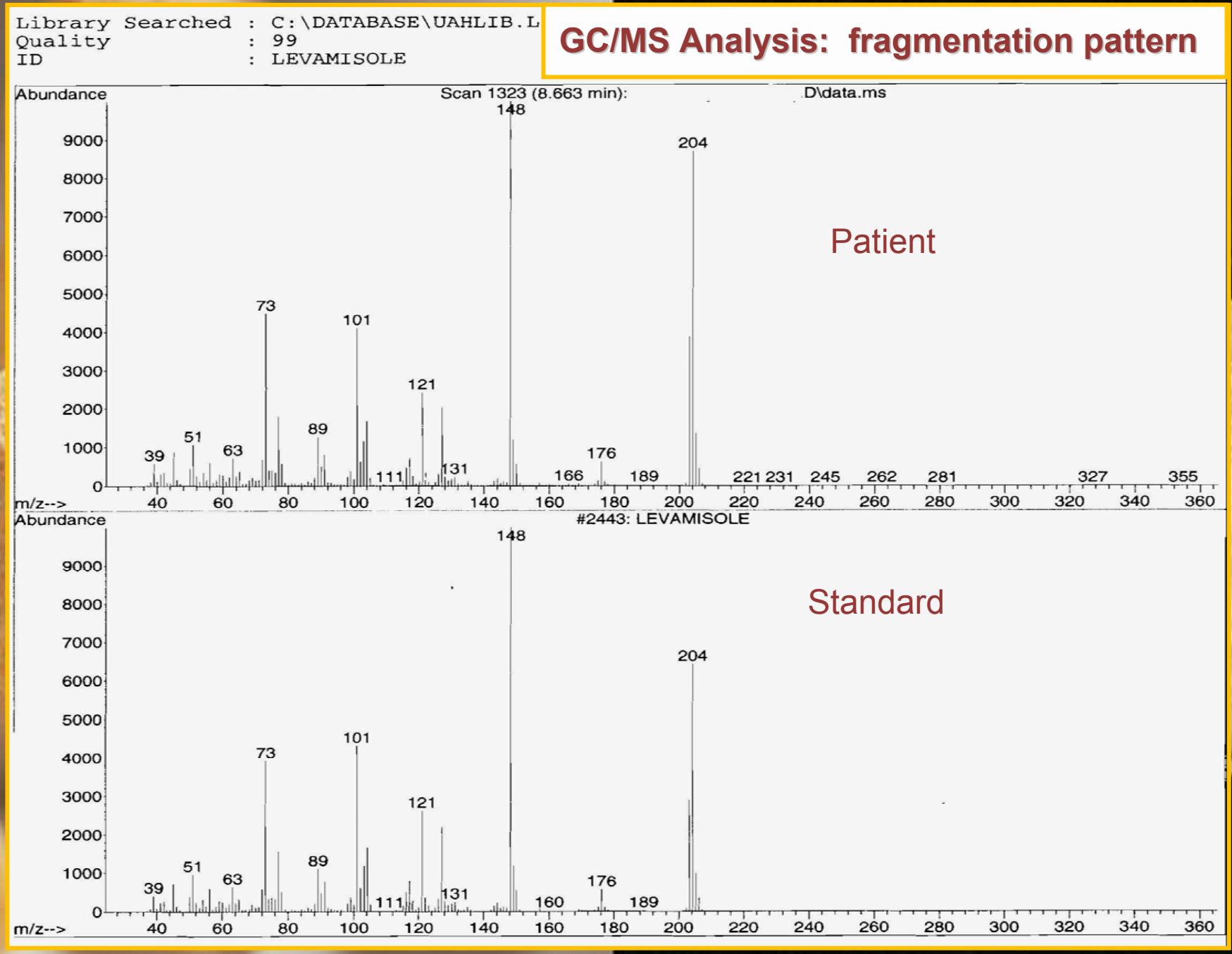
Data Acquisition

Data Interpretation/Verification

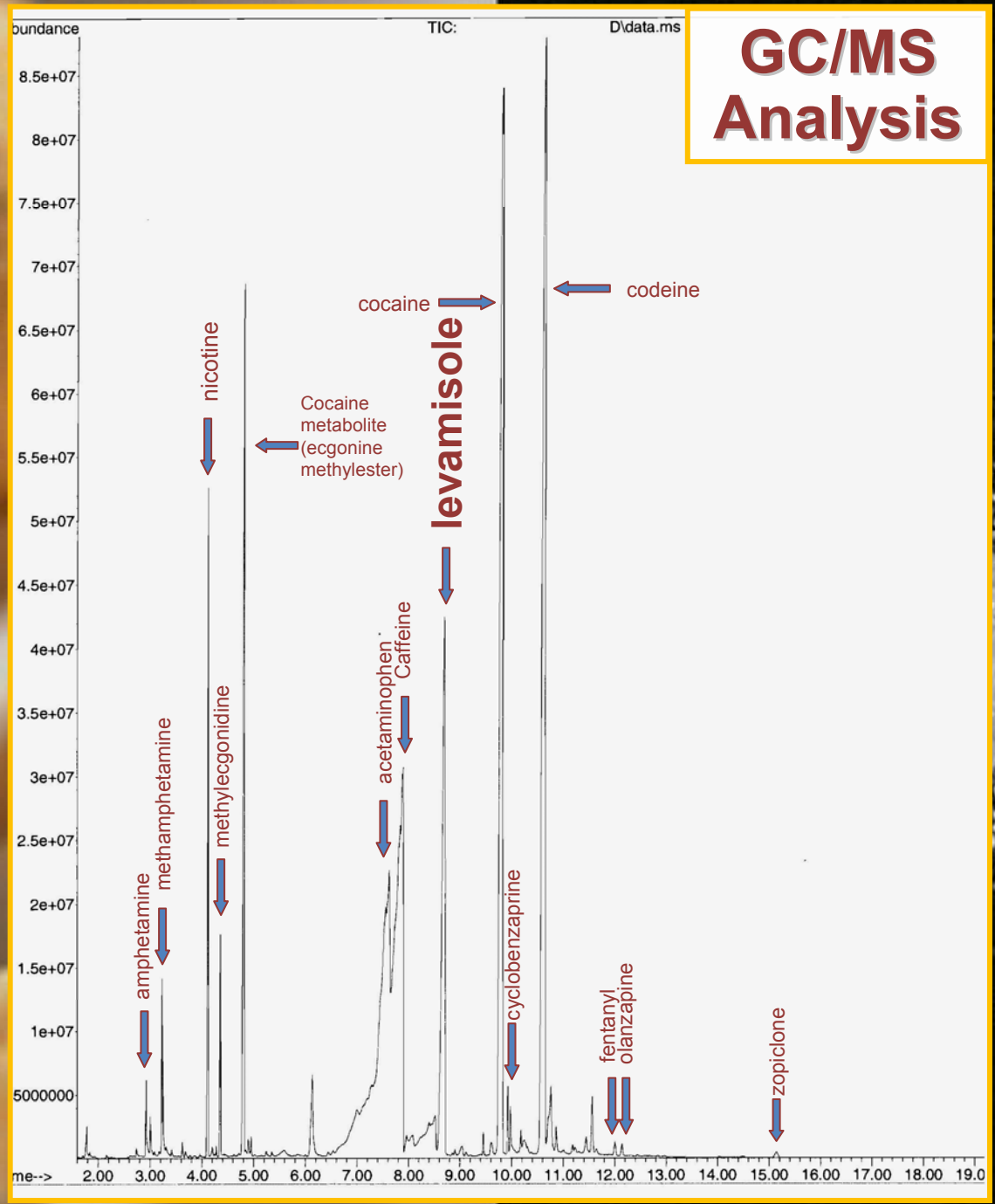
by comparison to authentic drug standards

1. Retention time (time to pass through system)
2. Fragmentation pattern (total ion mass spectra)

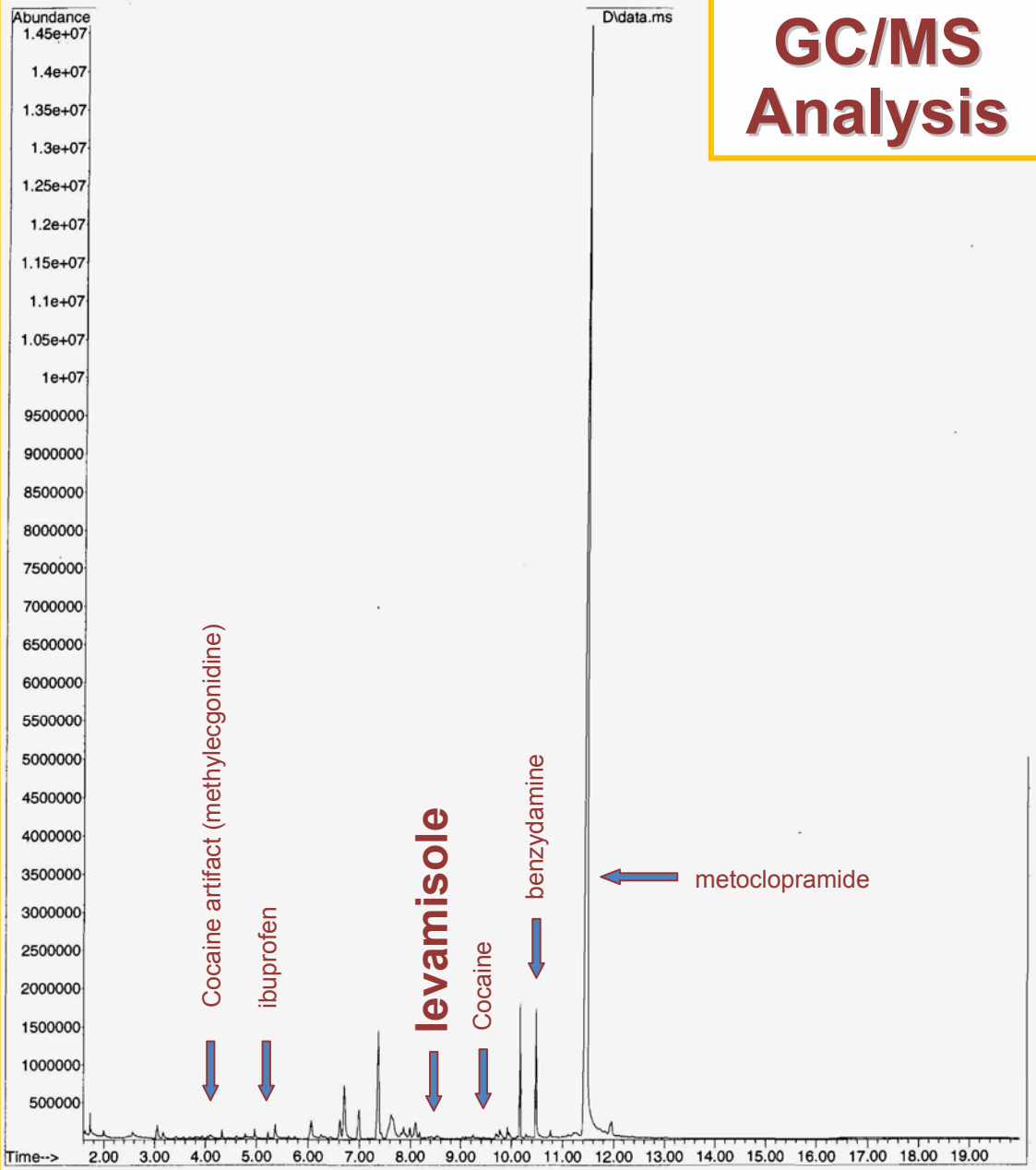
GC/MS Analysis: fragmentation pattern



GC/MS Analysis



GC/MS Analysis



Drug Detection Time in Urine

	Half Life	Drug Detection Time
Cocaine Metabolites	4 - 6.5 hours	3 days
Levamisole	5.6 hours	2-3 days
Methamphetamine	6 hours	2-3 days

1) J Anal Toxicol. 2002;26:393-400.
2) Cancer Chemother Pharmacol. 1998;41:477-84.

Levamisole Impurities

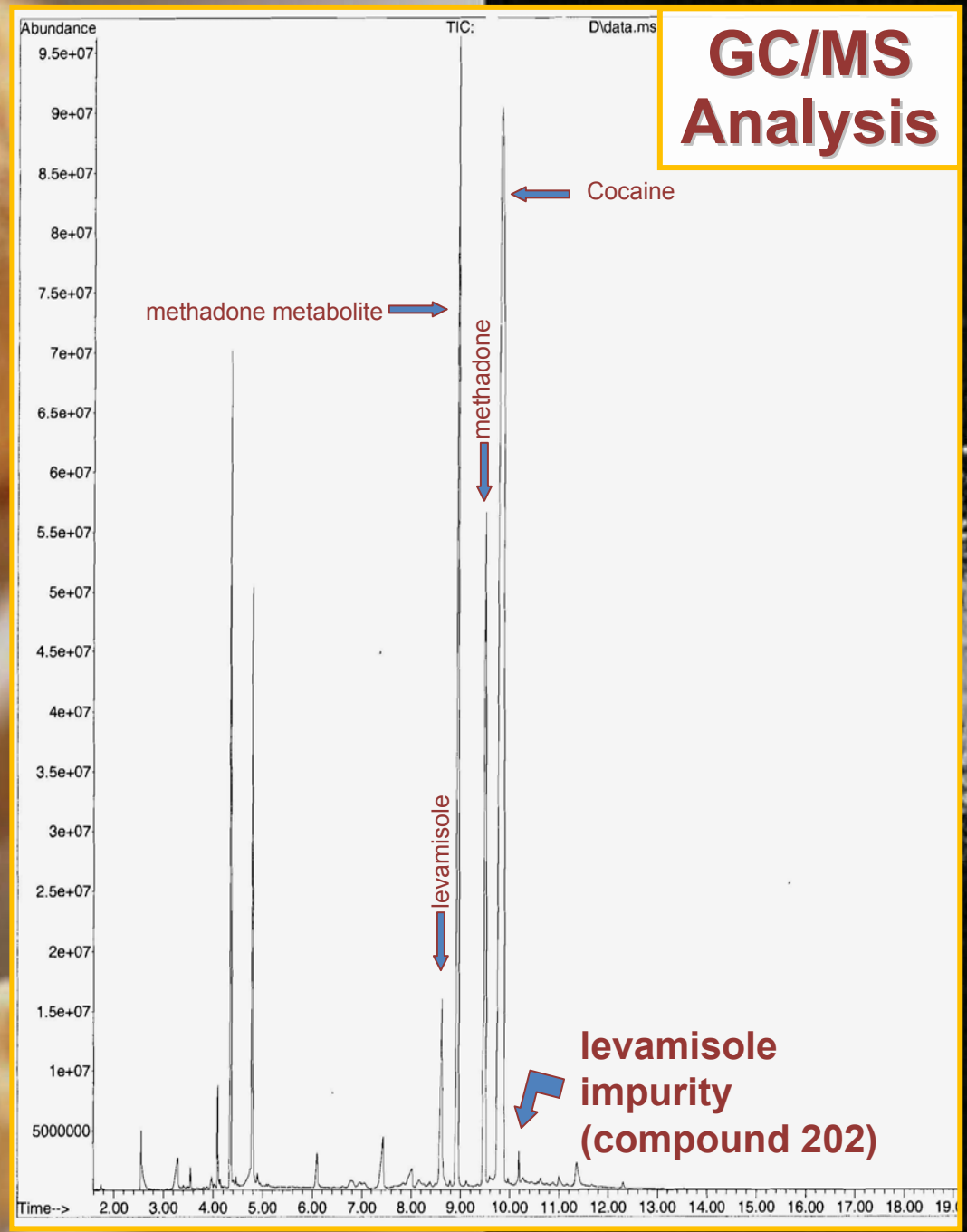
- Compound 202
  - synthetic by-product of pharmaceutical process
  - found in impure batches of levamisole
  - 6-phenyl -2,3-dihydroimidazo [2,1b] thiazole
- Compound 222
  - formed during the “crack process”

    cocaine HCL + $NaHCO_3$ + heat
  - 3 –(2-mercaptoethyl) -5-phenylimidazolidine-2-one

Both detected in urine specimens by GC/MS

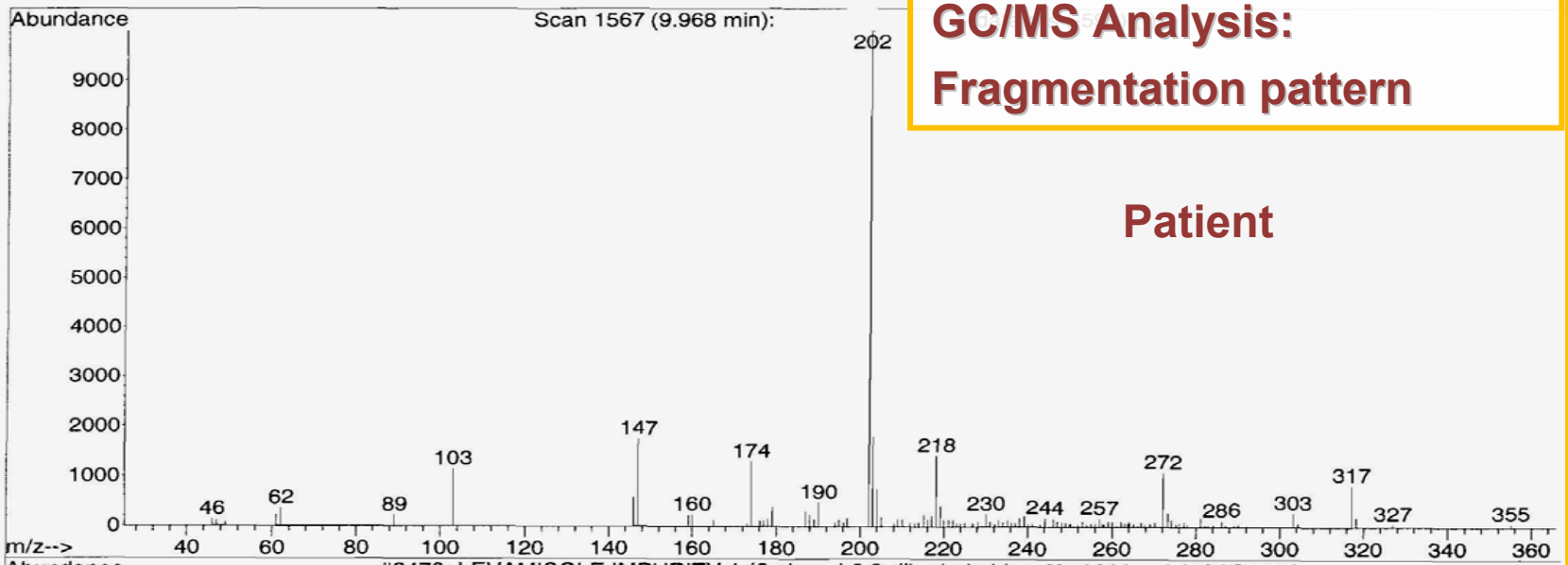
??? Toxicity/“Clinical” Effect ???

GC/MS Analysis

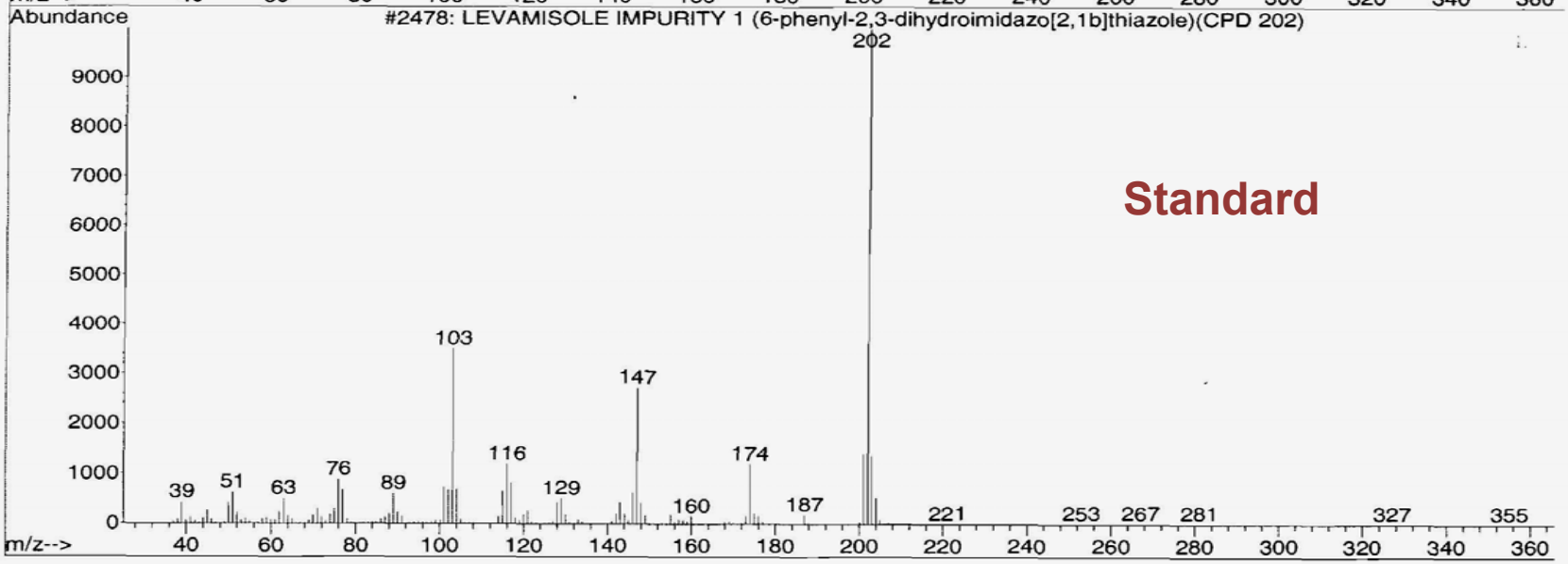


Library Searched : C:\DATABASE\UAHLIB.L
Quality : 64
ID : LEVAMISOLE IMPURITY 1 (6-phenyl-2,3-dihydroimidazo[2,1b]thiazole)(CPD 202)

GC/MS Analysis: Fragmentation pattern

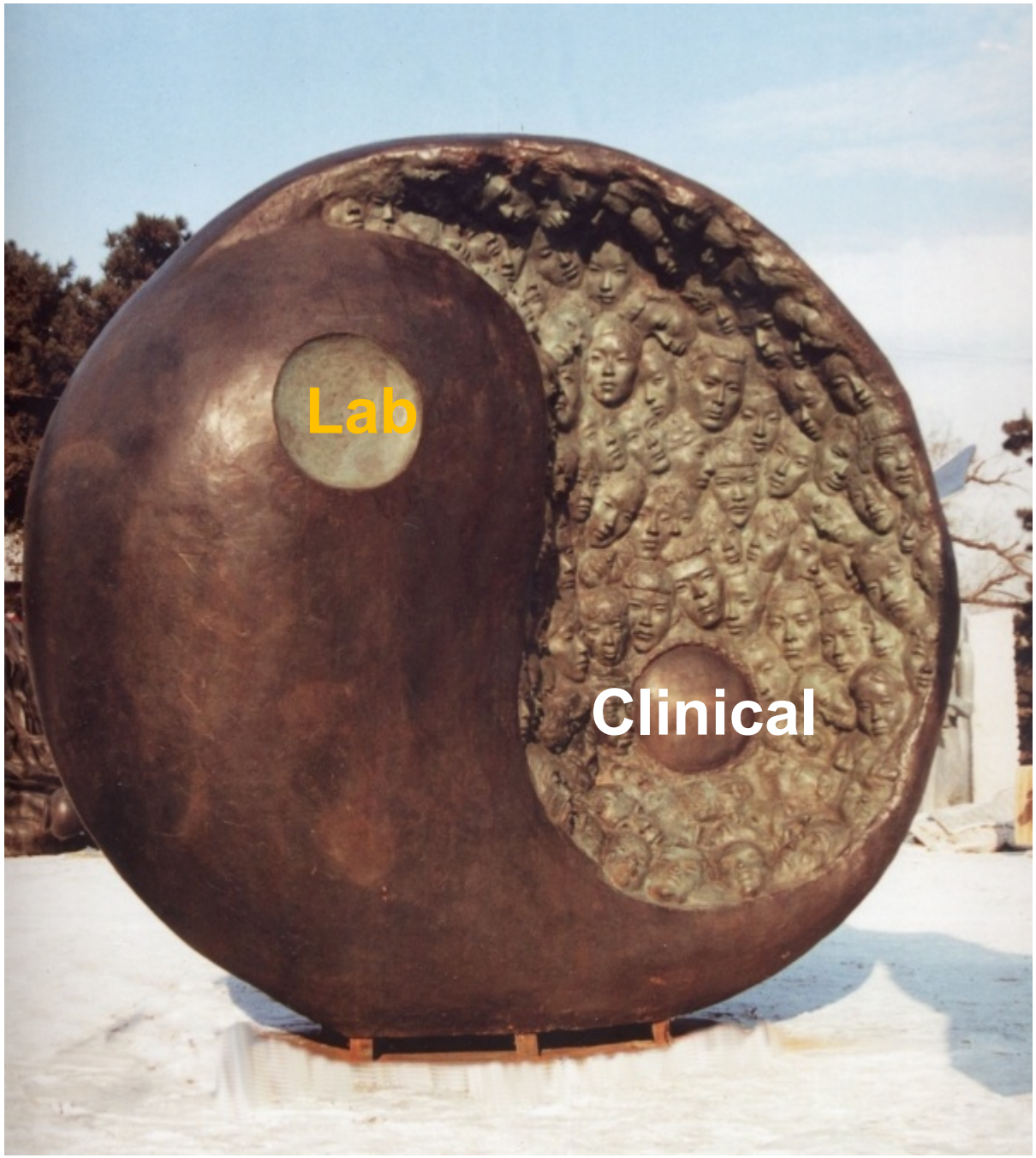


Patient



Standard


CENTIMETRES
Cat. No. 09-016
Fisher Scientific
Fisher Scientifique
INCHES/POUCES


Lab
Clinical

Annals of Internal Medicine

Established in 1927 by the American College of Physicians

LETTER

Agranulocytosis After Consumption of Cocaine Adulterated With Levamisole

▸ Nancy Y. Zhu, MD; Donald F. LeGatt, PhD; and A. Robert Turner, MD

17 February 2009 | Volume 150 Issue 4

Background: Levamisole is a veterinary antihelminthic previously used as an immunomodulator in rheumatoid arthritis and as adjuvant therapy in the treatment of colorectal cancer. It is no longer available in North America for human use but is available in the United States and South America for veterinary administration.

Since 2004, pharmaceutical agents have been found in cocaine supplies in North America and Europe (1). Levamisole contaminated 30% of cocaine seized by the U.S. Drug Enforcement Agency from July to September 2008 (U.S. Department of Justice, Drug Enforcement Administration. Cocaine Signature Program Report. January–October 2008. Internal document.) and 11% of cocaine samples tested in Alberta, Canada, from April to December 2008 (Office of Research and Surveillance, Health Canada. Personal communication.). Levamisole causes reversible agranulocytosis in up to 20% of cases (2), but the clinical effects of cocaine adulterated with levamisole have not been described.

		Urine		Blood Counts on Presentation				
Patient	Age and Sex	Levamisole & Cocaine	Other Positive Toxicology Findings	Neutrophil (x 10^9 cells/L)	Total WBC (x 10^9 cells/L)	# Days until Neutrophil > 1 x 10^9 cells/L	LAC	Clinical Complications
1	38 F	+	Morphine, lidocaine, fluconazole, dimenhydrinate/diphenhydramine	0	0.6	9	+	Cellulitis, pneumonia, bacteremia (*E.coli*)
		+	Methamphetamine, amphetamine, pheniramine, morphine, dimenhydrinate/diphenhydramine	0	1.2	8	+	*Cystitis (Klebsiella pneumoniae*), typhilitis
2	41 F	+	Lidocaine, zopiclone, 8 chlorotheophylline, dimenhydrinate/diphenhydramine	0	2.2	5	+	None
3	18 F	+	Metoclopramide, benzydamine, ibuprofen	0	0.6	6	+	Thrush, peritonsillar abscess, cellulitis
4	44 F	+	Acetaminophen, ketorolac, chlorpheniramine metabolite, thymol, polyethylene glycol, dimenhydrinate/diphenhydramine	0	0.7	20	+	None
5	48 M	+	Clindamycin	0	0.5	7	+	Parotitis, face & neck cellulitis, intubation with ICU admission for airway protection

Findings

- Isolated agranulocytosis → neutrophil 0
- Recent cocaine exposure
- Previously healthy
- Vitamin B12 normal, Folate normal
- Other causes of neutropenia ruled out:

  - rheumatologic diseases
  - malignancy
  - medications
  - nutritional deficiency

Lupus Anticoagulant

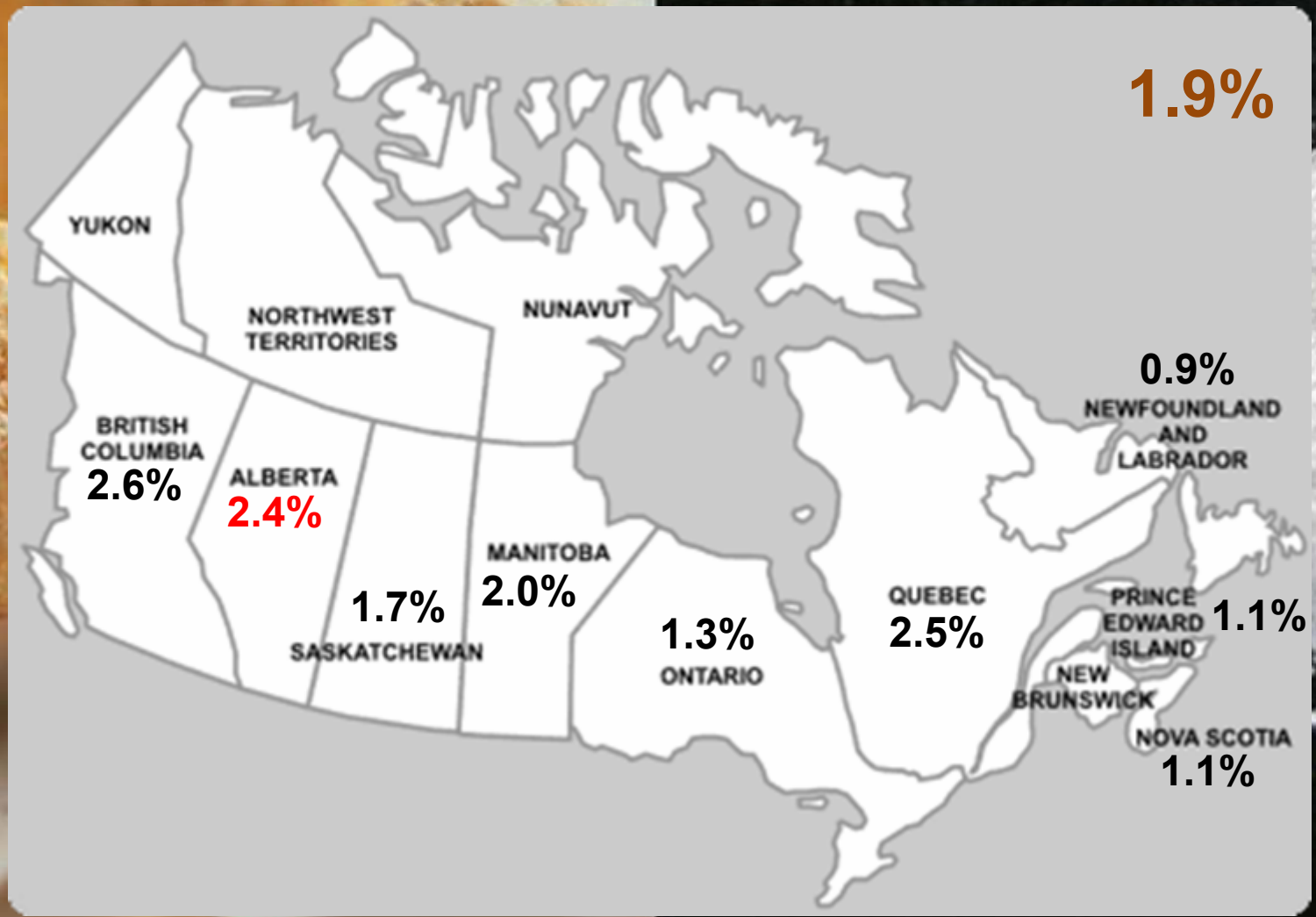
- Acquired Antiphospholipid antibody
- Can be transiently induced by viral infections
- Seen with chronic levamisole use
- Appears to be chronic
- ? ↑ risk of thrombosis

Br J Dermatol. 1999;140:948-51.

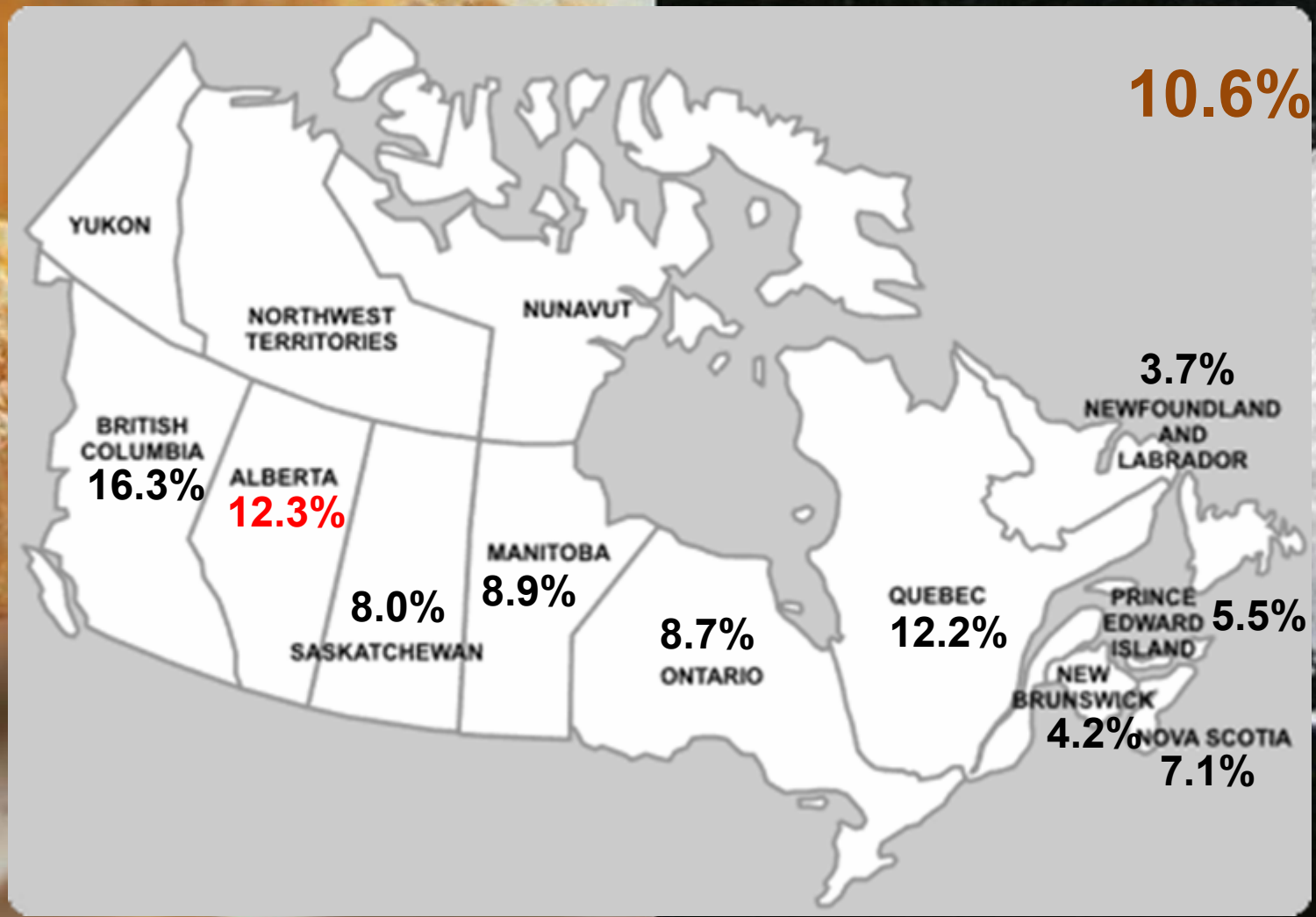
Limitations

- Direct causation:
  - Did the levamisole come from the cocaine?
  - Did the levamisole cause the agranulocytosis?
    - In vitro stem cell growth
  - Was there another agent not detected causing the agranulocytosis?
- Specific characteristics at risk?
  - HLA-B27, rheumatoid arthritis

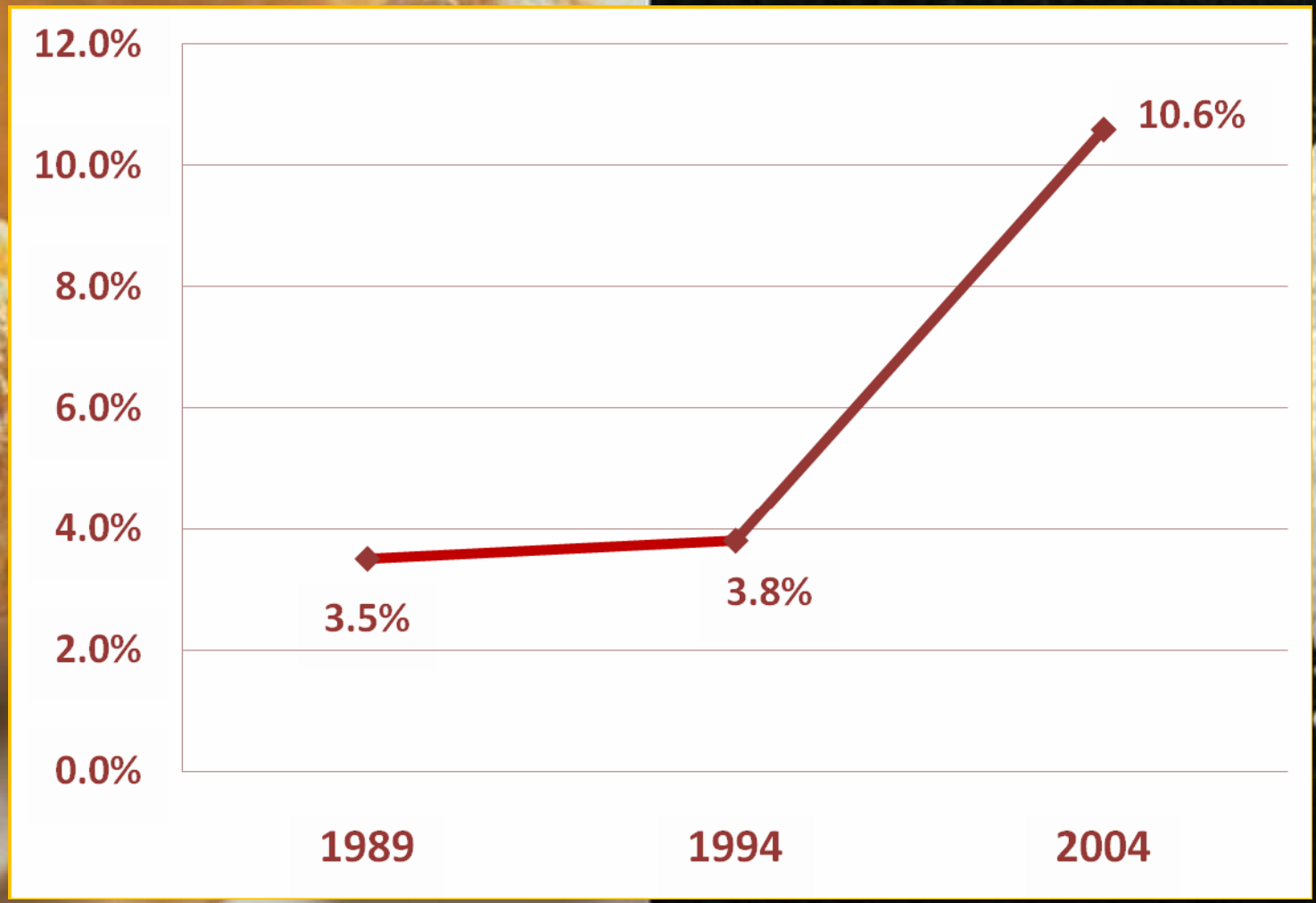
Canadian Addiction Survey 2004: Cocaine Use in the Last Year



Canadian Addiction Survey 2004: Cocaine Use in Lifetime



Canadian Addition Survey 2004: Cocaine Use in Lifetime



The Alberta Response

Nov. 21, 2008: Province-wide alert to physicians

Nov. 28, 2008: Public health advisory

Neutropenia related to levamisole adulterated cocaine
(**Quick Response Sheet** for physicians)

http://www.capitalhealth.ca/EspeciallyFor/HealthProfessionals/default.htm

Alberta Health Services

Public Health Division
Medical Office of Health

Neutropenia related to levamisole adulterated cocaine
QUICK RESPONSE SHEET

What to look for:

- Any signs of infection, including fevers. Including any skin, abscess or lung infections that appear to have developed more rapidly or have progressed more seriously.
- Suspected cocaine use.

Diagnostic Tests:

- Urgent CBC and differential to look for neutropenia.
- A spot urine specimen (minimum 10 mL) should be collected for cocaine metabolites and levamisole toxicology testing **as soon as possible** – the latter drug has a short detection window in urine (ideally specimen should be collected within 24-48h of use).

Specify "**neutropenia**" and "**levamisole toxicity suspected**" in the *Clinical information* section of the requisition. Contact your referral toxicology laboratory if more information is required.

Treatment:

If the neutrophil count is less than 1.0 and the patient is febrile or has an active infection, **an urgent referral to an on-call Hematologist** should be made.

The patient will require admission to hospital immediately, an infectious work-up including blood cultures should be undertaken and broad-spectrum intravenous antibiotics (ie. Piperacillin/Tazobactam, Imipenem or Ceftazidime) administered. Filgastrim (G-CSF) should be started until consultation with a hematologist has been made. An additional investigation that can aid in the diagnosis is an elevated aPTT from a lupus anticoagulant which has been seen as well.

Recovery generally occurs after 7-10 days, but close monitoring is required as the risk of mortality from sepsis is high.

Interviews with Client:

Advise clients that the cocaine being sold is potentially cut with a dangerous substance that could harm their immune systems. If possible, inquiry about client's cocaine use practices, specifically related to the last time they used.

- **Type of cocaine use:** □ **Crack** □ **Powder**
- **Method of cocaine use:** □ **Smoke** □ **Inject** □ **Snort**
- **Amount of cocaine use:** **Number of grams used: _____**
  Number of days used: _____
- **Did the cocaine have a unique taste, smell or look to it?**
- **Do they consistently use the same drug supplier?** □ **Yes** □ **No**
- **Amount purchased from last supplier:** **Number of grams: _____**

Contact Public Health Department:

If clinicians become aware of any more cases, contact public health with the patient's name, date of birth, PHN, address and phone number as we are monitoring the situation. Contact: Lewinda Knowles (780) 413-7740.

Levamisole Comment Appended to Patient results

"Caution: Levamisole, a cocaine cutting agent, can cause acute, profound NEUTROPENIA. If this is the case, please contact Alberta Health Services, Public Health Division, 780-413-5034."

Latest Alberta Update
June 2009

- Confirmed Cases: 13
- Probable Cases: 32
- Other jurisdictions:
  - British Columbia
  - Colorado
  - New Mexico
  - Washington

Why Levamisole??

- Answer(s) remain elusive
- Theories:
  - May function as CNS stimulant:
    - Ganglion nicotinic acetylcholine receptor agonist[1]
    - Elevated dopamine and endogenous opiate levels (codeine, morphine) in various brain regions (rat)[2]

1. Davis FL et. al., eds. *Neuropsychopharmacology: the fifth generation of progress.* Philadelphia: Lippincott Williams & Wilkins, 2002.
2. Spector et. al. Neuropsychophamacology 1998; 19(5): 417-27.

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