

Volume IV Orientation and Training	ORA LABORATORY MANUAL FDA Office of Regulatory Affairs Office of Regulatory Science	<small>DOCUMENT NO.: IV-14</small> <small>VERSION NO.: 1.5</small> <small>FINAL</small> <small>EFFECTIVE DATE:</small> <small>10-01-03</small> <small>Revised:</small> <small>02-14-13</small>
Section 14	COMPLAINTS & TAMPERING	Section 14

Contents

14.1	Objective
14.2	Introduction
14.3	FDA Laws and Regulations
14.4	Preliminary Information and the Analytical Strategy
14.5	Safety
14.6	Sample Handling
14.7	Initial Observations
14.8	Analytical and Instrumental Methods
14.9	Analytical Documentation
14.10	Reporting References
14.11	Document Change History

14.1 Objective

To provide a framework for the analysis of samples which are obtained during the investigation of consumer complaints or which are associated with alleged instances of product tampering.

14.2 Introduction

The Agency's consumer complaint system is a crucial source of information on potentially unsafe products in the US marketplace. Complaints involving death, serious illness, or injury are given the highest priority and demand an immediate response. Complaints about infant formula, baby food and medical foods are especially sensitive due to the vulnerability of the population that consumes these products. Evaluation of injury/illness complaints having to do with dietary supplements is important to the Agency for regulation and protection of the consumer from unsafe supplements. Product tampering is an intentional adulteration of a product that is frequently brought to the Agency's attention by a consumer complaint.

Laboratory examination and analysis of complaint/tampering samples will allow the Agency to assess the severity and scope of the potential problem. Analytical results are fundamental to development of a response that will minimize risk to the public.

Note: This section is intended to be used as a whole. Critical information may be overlooked if individual sub-sections are read out of context.

14.3 FDA Laws and Regulations

A complaint serves as notification that a product in commercial distribution may be in violation of FDA laws and regulations. (1)

FDA is authorized to investigate reported tampering of FDA regulated products under the Federal Anti-Tampering Act, Title 18, USC, Section 1365. Note that the act not only makes tampering a crime but also identifies as criminal “whoever knowingly communicates false information about product tampering” and “whoever threatens.” The Office of Criminal Investigation (OCI) has the primary responsibility for all criminal investigations of tampering/threat incidents. (2, 3)

14.4 Preliminary Information and the Analytical Strategy

Many complaints allege product tampering; however, frequently facts uncovered during the investigation do not support the allegations. Prior to laboratory examination and analysis (unless there is prevailing investigational information), it is difficult to differentiate manufacturing problems from intentional tampering. Consequently, the analytical approach is usually the same for both.

There are three distinct scenarios in which a product may be adulterated:

1. During manufacture as the result of error, accident or sabotage.

Examples of instances initially thought to be tampering (because only a few units were affected) but were eventually linked to manufacturing problems include the following: contamination of a product with cleaning solution due to incomplete rinsing of processing equipment, foreign objects such as metal fragments or machine parts present in the product due to equipment failure, and an incorrect product inside a container due to labeling mix-ups.

2. During distribution as the result of a tampering, the product is often disguised or covered up so that the product appears “normal”.

The most infamous example is the 1982 case in which seven people in the Chicago area died after taking Tylenol capsules poisoned with cyanide

3. After the product is in the possession of the consumer.

Examples are the “copy cat” or false report cases that may follow a highly publicized tampering. Intentional poisoning of a person is another example of this tampering scenario. There can also be instances in which the consumer unknowingly contaminates the product himself/herself. One example is when the suspicious tablets or capsules found in a beverage are the same as the tablets or capsules the consumer was attempting to swallow some time prior to the “discovery”.

The objective of the investigation and analysis of complaint/tampering samples is as follows: determine if the product is adulterated or substandard; determine the nature/identity and extent of the adulteration; and evaluate, if possible, which of the three adulteration scenarios listed above is most likely and/or which, if any, can be ruled out. This assessment represents an ideal situation. In reality, the ability to resolve these issues with absolute certainty is often limited by the details of the complaint, as well as the history and condition of the sample received by the laboratory.

Prior to starting the analysis:

Obtain as much background information as possible. Read the complaint form, collection report and affidavits and discuss the sample with the investigators. At this point it is important to differentiate facts from allegations and theories. Facts are when a product was manufactured (as determined from code/lot number/expiration date) and when the complaint was made. Allegations, e.g. statements the product tasted bitter or made the consumer nauseous, may or may not be accurate or true. Information obtained from the manufacturer on previously encountered packaging or product defects is beneficial. Medical records can provide important clues in cases involving death, serious illness, and injuries. For example, medical tests may indicate that the consumer ingested a reversible cholinesterase inhibitor in which case it would be sensible to screen the sample for carbamate pesticides. Some guidance in this area can be obtained from toxicology texts (4, 5) or through consultation with local Drug and Poison Information Centers or toxicology laboratories.

Whenever possible, obtain a control sample of the product for comparison to the suspect sample. For the most meaningful comparison, the control should closely match the suspect with respect to product, packaging, manufacturing location, and time. There should also be some assurance that the control is intact and free of contamination. In the absence of a well-matched control, one

alternative is to use a sample with nominally the same suspect sample matrix as a comparison control for chemical tests.

General guidance on the examination of materials for forensic purposes can be found in an excellent collection of monographs (6, 7, 8).

The FDA Forensic Chemistry Center (FCC) located in Cincinnati, Ohio, has extensive experience in dealing with product tampering samples. Contact them whenever there are questions about the approach to the analysis, the methods to use, or whether the FCC has prior experience with the type of complaint/tampering situation under investigation.

Forensic Chemistry Center:

Phone 513/679-2700

FAX: 513/679-2761

<http://inside.fda.gov:9003/ORA/CentralRegion/ForensicChemistryCenter/default.htm>

14.5 Safety

Treat complaint/tampering samples with extra precaution because they may present unidentified/unforeseen hazards. Background information from the complaint form and collection report may help the analyst anticipate hazards. Initial examination may involve hazards from a number of sources including biological (e.g., blood-borne pathogens like HIV); chemical (e.g., cyanide or toxic or carcinogenic compounds); and/or physical/mechanical (e.g., needles, syringes, razor blades, etc.). Choose with care the laboratory location or analysis site for the suspect sample. Consider the use of biological safety cabinets, chemical fume hoods, sealed glove boxes, etc. Personal protection should include safety glasses, protective gloves, respiratory protection (if needed), and protective clothing ranging from laboratory coats to protective safety suits and face shields. Before starting the initial examination all containment, clean up and disposal supplies should be ready and on-hand. Special care should be exercised if any odors, leakage or discoloration associated with the sample container are noted. Be aware that some adulterants may react with the product containers and alter the sample if the sample is not transferred to a resistant container for storage. Suspect samples should only be examined/analyzed when other trained laboratory personnel can monitor the analyst in the event of an accident.

Although detectable odors may be unavoidable; organoleptic testing, i.e., purposefully smelling the sample, should only be done if it is known that it is safe to do so. Even in this event, exercise extreme caution. *Do not, under any circumstances, taste the sample!*

14.6 Sample Handling

It is important that judicious attention to detail occur in the handling of complaint/tampering samples in order to maintain sample integrity and avoid overlooking or damaging evidence. Carefully document chain of custody and storage conditions. Preserve as much suspect material

as possible and preserve forensic evidence. Unless otherwise notified by submitting officials, protect fingerprint evidence by wearing cloth gloves over vinyl gloves or latex gloves and using tongs or forceps for handling the sample on edges, seams, and corners (i.e., away from potential fingerprint regions). As much of the packaging and product as possible should be left undisturbed. It is imperative to document every step of the examination and every observation in writing as well as by photodocumentation (film or digital photography or imaging).

(Important!) Obtain a gross sample weight, (liquid or solid) before proceeding with the analysis. The sample may be weighed in the original container and the container weight subtracted later, if needed. The weight/volume may be needed for comparison to control samples, to determine the amount of product remaining, or to substantiate the amount consumed, etc.

Only one suspect sample should be processed at a time. A clean, new piece of evidence paper (roll paper, butcher paper, etc.) with the sample identification on one corner should be placed at the examination site. If the sample examination did not cause visible particles or residues to fall onto the paper, the paper can be discarded before proceeding with the analysis of other samples. If particles or residues are observed, fold and retain the paper with the sample.

Intact suspect sample cartons, boxes, bags, plastic film covers, etc. should be opened in a region that is not suspected as being the site of entry. Avoid opening along manufacturer seams or seals. Record and document any observations and sample treatment used in the examination of suspect samples.

Perform a thorough non-destructive physical examination (see Section 14.7) before proceeding to chemical analysis (Section 14.8). There may be a point where it is best to stop the examination and refer the sample to another law enforcement agency/lab with more familiarity with forensic techniques for some analyses such as lifting of fingerprints, matching glues, identifying particles in situ, etc. Any suspicious findings should immediately be discussed with lab management to determine a best course of action.

When sampling any portion of the suspect sample for analysis, use as little sample as possible to conserve the sample for confirmatory analysis or further tests that may need to be run by other specially equipped laboratories such as the Forensic Chemistry Center. Assure that the condition of the sample has been well documented before sampling. Ordinarily, the sample should not be homogenized. For example, if the sample consists of a liquid in a bottle with some particulate on the bottom, remove a portion of the liquid and remove a portion of the particulate and analyze them separately.

14.7 Initial Observations

The observation process should proceed in a logical manner working inward from the external surfaces, only opening the product container after all external examinations are completed. Written and photodocumentation of the suspect product should be provided for the container

(box, carton, package, wrapper, bottle, etc.) and any other sample related items. Photodocumentation may include the use of standard 35mm film photography, digital camera photography, computer-operated scanner, CCD cameras coupled to computer controlled image capture devices, and even radiography. Include a legible measurement scale (preferably metric units) in every photographic image (regardless of media). Examination may include visual observations using the unaided eye and closer examination using a hand lens, stereoscopic light microscopy (SLM) and/or compound light microscopy. The suspect sample should be examined by short-wavelength and long-wavelength ultra violet light and/or a variable frequency light source (e.g., Crimescope®) and all findings documented.

Control samples should be processed by the same procedures used for the suspect sample; any discrepancies are noted and documented. Record the manufacturing code and any codes printed on the labels, containers, and closure systems for both the suspect and the control.

Any odors detected should be immediately investigated before proceeding in order to prevent exposure to toxic vapors or gases. (See Section 14.5, Safety)

Check for any surface anomalies such as punctures, tears, cuts, holes, slits, abrasions, etc. Thoroughly examine all container closure seams, folds, crimps, caps, tops, lids, liners, etc. and note any irregularities. Document the condition of tamper evident closures such as safety seals, tear away ring bottle caps, etc. Look for chips or cracks in glass and damaged threads on screw caps. Packaging joints and seams should be closely examined for excess glue, glue smears, glue tear pattern, multiple glue types, etc. Any extraneous surface marks in paint, ink, pencil, marker, scratches, etc., should be documented. Note any discoloration, dust, powders, crystals, debris, or leakage. Evaluate the product for color, clarity, fluidity, layering, clumping, marks, chips, stains, orientation (e.g., capsule parts askew, units out of place in a sectioned package) and foreign objects, etc.

The location of any unusual findings or foreign objects should be diagrammed and photo documented. Removal of any portion of the suspect sample should take place only after the initial observations and photodocumentation have been completed. Once photographed in situ, the object or questionable portion of the sample may be isolated for additional characterization and/or chemical analysis.

Analysis of any observable foreign objects, foreign material or observed non-homogeneity may include characterization and chemical analyses by computer assisted image analysis, scanning electron microscopy with energy dispersive x-ray analysis, polarized light microscopy, FT-IR or some other technique.

14.8 Analytical and Instrumental Methods

I. Simplify the problem if possible

If the preliminary information indicates that a certain contaminant (or type of contaminant) is present, then analytical efforts should target that material. Initial observations and odors can provide important clues. For example, the odor of the sample may suggest the presence of bleach, ammonia, amines or a petroleum product such as gasoline, thinner or a vehicle for an emulsifiable concentrate of a pesticide. Analytical methodology can be obtained from compendia (9, 10, 11) or the general chemical literature (12, 21) but often these procedures are modified to accommodate differences in the sample matrix. The analyst may need guidance from an experienced analyst for method modifications and validations. Method validation studies will demonstrate the method is usable to support the conclusions of the analysis for the sample and the situation to which it was applied.

II. When there isn't much to go on

The remainder of this section addresses situations where there is little information to provide focus for the analyst.

If moderate shaking of the sample (see Section 14.6 before shaking) produces a persistent foam, then the presence of a surfactant which might be associated with a cleaning product is indicated. If the foam remains when a small portion of the sample is acidified, then the surfactant is probably a detergent. This form of tampering is relatively common and there are a variety of tests to determine which class of surfactant is present (13, 14). A soap is indicated when the foam produced by moderate shaking does not remain after acidification.

Exposing the sample to ultraviolet light may indicate that a component of the contaminant is a fluorescent material like many of the dyes which are associated with antifreeze. This would suggest that the sample be further examined for the presence of ethylene glycol.

A good early chemical test is an estimate of pH with test paper (e.g. pHydrion paper (1 to 12), MicroEssential Laboratory or colorpHast pH 0 –14 strips). A shift in pH relative to a control sample indicates a change in the sample which should be explored. If the pH is less than 2 or greater than 10, then the presence of a corrosive acid or base is likely. Further investigation might include examination by ion chromatography (IC) for anions, such as chloride or nitrate, or inductively-coupled plasma atomic emission spectroscopy (ICP-AES) or mass spectroscopy (ICP-MS) to indicate the presence of a metalloid and/or complex anion (such as PO_4^{2-}). IC can also be used to detect some organic acid; gas chromatography – mass spectrometry (GC-MS) can be used to detect organic acids or bases.

Other simple chemical tests might include cyanide screen (Cyantesmo test paper) and sulfide screen with lead acetate paper.

Spot tests for the presence of oxidizing agents using diphenylamine in sulfuric acid (15) or Starch/Iodide paper can provide useful information.

Experience with actual tampering cases has shown that the contaminant is typically present in relatively large amounts. However, when the examination reveals no remarkable differences, it is important to have a sense of the adequacy of the screening procedure. The toxicity of a wide variety of substances has been described based upon ranges for the probable oral lethal dose (4). If we allow for a margin of safety of 3% of the probable oral lethal dose, then a warning concentration for a contaminant in a product can be defined by the following equation:

$$\text{Warning Concentration (mg/ml)} = 0.03 \times \frac{\text{Probable Oral Lethal Dose (mg/kg body wt.)}}{\text{Body Weight (kg)}} \times \frac{1}{\text{Portion (ml)}^{-1}}$$

Using a body weight of 70 kg (average adult) with a portion size of 355 mL (e.g. a 12 oz. beverage), the table below can serve as a guide to the needed sensitivity of the analytical methods. Bear in mind that significant clinical illness can be expected at doses on the order of 10% of the probable lethal dose. This equation can be adjusted in keeping with additional information. For example, there may be a good estimate of the amount of product ingested by a child of known body weight and an identified poison with a known lethal dose may be suspected.

Description	Toxicity Class	Probable Oral Lethal Dose (mg / kg body wt.)	Warning Concentration (mg/l)
Non-toxic	1	> 15000	
Slightly Toxic	2	5000 to 15000	30000
Moderately Toxic	3	500 to 5000	3000
Very Toxic	4	50 to 500	300
Extremely Toxic	5	5 to 50	30
Super Toxic	6	< 5	1

NOTE: The minimum lethal dose for some super toxic materials can be as low as 0.1 (mg/kg body weight) and this is used to calculate this number.

III. Application of instrumental techniques

The following is a brief overview of the use of instrumental methods to compare the suspect sample and the control sample. It is recognized that not all of the instrumentation that will be discussed is found in every laboratory. A basic understanding of each technique on the part of the analyst is assumed.

Sample preparation should be minimized in order to speed the progress of analysis and to retain information. Whenever possible, direct analysis is preferred to extraction/clean-up. Good judgment on the part of the analyst(s) should be exercised when deciding which methodologies are to be used and the order in which selected methodologies should be executed.

A. Static Headspace Sampling combined with Capillary Gas Chromatography - Mass Spectrometry (GC-MS) for Volatile Materials

The technique (16) is directed at the detection and characterization of volatile materials (boiling points approximately below 200°C). It is very useful for detecting solvents (e.g. alcohols, chlorinated hydrocarbons), fragrances associated with cleaning products which frequently appear as contaminants, and petroleum products. Petroleum products may occur as contaminants in their own right or may be associated with pesticides in emulsifiable concentrates.

A small portion (10 to 500 mg) of the sample is placed in a vial which is sealed with a teflon-lined septum-cap. The vial is incubated at an elevated temperature for about 10 min and a portion of the vapor in the vial (the headspace) is withdrawn through the septum and injected into the GC-MS for analysis. Limit of Detections (LODs) for typical analytes extend to the low mg/kg range.

Mass spectra which are associated with observed differences between the suspect sample and control sample are compared to reference spectra (17) to obtain tentative identification. This may be subsequently confirmed and quantified through the analysis of standards and demonstrated recovery of a standard which has been spiked into the control sample.

B. Capillary Gas Chromatography with Mass Spectrometry (GC-MS) for Volatile and Semi-volatile Materials

Direct injection of the sample or an extract/solution of the sample in methanol is the first choice.

If the nature of the sample precludes this or if some pre-concentration is needed, then the sample may be extracted with acidified aqueous acetonitrile (pH = 3) and the acetonitrile subsequently isolated by "salting out" for analysis by GC-Flame Ionization Detector (FID) or GC-MS.

Isolation of a basic extract is obtained using the same procedure with basic aqueous acetonitrile (pH = 10). Additional sensitivity can be obtained by evaporative concentration of the acetonitrile

extracts. This protocol is modeled upon a multi-residue pesticide method (18) in conjunction with an extraction procedure from a guide to forensic analysis of pharmaceuticals (15).

The range of applicability can be extended to functionally non-volatile materials by silylating the extracts after solvent exchange into pyridine by the addition of N,O-bis-(trimethylsilyl)-trifluoroacetamide which contains 1% trimethylchlorosilane with incubation at 60 degrees C for at least 15 min and repeating the analysis.

The suspect sample and the control sample are compared to expose differences. The mass spectra associated with these differences are compared to reference spectra to provide tentative identification. Occasionally, the tentative identification proceeds from first principles (19).

C. Ion Chromatography (IC)

The role of this technique is to detect anions such as those in the table, below. There is some overlap with GC-MS and Inductively-Coupled Plasma (ICP) methodology but ICP occupies an important niche. Unless circumstances dictate otherwise, analysis of a sample is performed on a ten-fold dilution of the sample in water using a conventional anion column (eg. Dionex AS9-HC, or equivalent) in suppressed mode with a 9 mM sodium carbonate buffer. Additional sample preparation such as further dilution or the use of sample preparation cartridges such as C-18, Ba (for sulfate removal), or H+(neutralization) may be needed for some samples. More sophisticated chromatography such as the use of hydroxide gradients may be needed with the most complicated samples. It is worth noting that a reactive contaminant, such as bleach, may produce additional peaks in a suspect sample that can only be properly characterized through additional experiments which monitor the impact of the addition of the nominal contaminant to a control sample through time. The probable presence of bleach in the suspect sample at some point in time is implied by elevations in the chloride and chlorate levels along with high pH and the presence of excess sodium.

Some Potentially Toxic Anions and the Associated Warning Level (WL)

Toxicity Class 6	Toxicity Class 5	Toxicity Class 4
WL = 1 mg/l	WL = 30 mg/l	WL = 300 mg/l
Azide	Bromate	Chlorate
Fluoroacetate	Fluoride	Fluoroborate
	Fluosilicate	Iodate
	Nitrite	Lactate
		Oxalate
		Thiocyanate
		Thioglycolate

D. High Performance Liquid Chromatography - Mass spectrometry (HPLC-MS)

A wealth of methodology using HPLC and Thin Layer Chromatography (TLC) for analyzing certain compounds or classes of compounds is found in compendia (10, 11) and selected references (15). However, because of reduced information content of UV-Vis spectra with respect to MS data, HPLC techniques are somewhat inefficient for general screening. Advances in the application of mass spectrometry to liquid chromatography have made HPLC-MS the method of choice for detecting non-volatile or thermally unstable compounds (e.g. cardiac, glycosides, alkaloids, proteins) which are not amenable to determination by GC-MS. HPLC-MS is especially useful as a screening tool if a comparison sample is available. There are some restrictions on mobile phase composition which must be considered, and interpretation of results requires a degree of skill and experience due to lack of spectral libraries for HPLC-MS.

E. Inductively-Coupled Plasma Atomic Emission Spectroscopy (ICP-AES) for the Detection of Metals, Metalloids and Some Complex Anions

Many liquids and some water soluble solids can be analyzed directly, or with a single dilution, by ICP-AES and ICP-MS. However, in general, samples are solubilized or digested to remove organic components with concentrated acid. Modifications may be needed to digest the sample properly in order to detect certain elements (e.g. Hg). (20)

Selected Metals with Toxicity Class and Warning Level (WL)

Toxicity Class 6	Toxicity Class 5	Toxicity Class 4
WL = 1 mg/l	WL = 30 mg/l	WL = 300 mg/l
Arsenic	Antimony	Boron
Selenium	Barium	Cobalt
	Cadmium	Copper
	Chromium	Gold
	Mercury	Lead
	Silicon	Lithium
	Tellurium	Manganese
	Thallium	Nickel
	Tin	Zinc
	Vanadium	

The form of the element defines its toxicity. This can create difficulties in the interpretation of comparative results and limit the usefulness of elemental analysis in some cases. For example, Phosphorous as Yellow Phosphorous (Toxicity Class 6) is a significant hazard but Phosphorous as Phosphate (Toxicity Class 3) is commonly encountered in foods. Inorganic arsenic is highly

toxic (toxicity class 6), but arsenic as arsenobetaine, which is found in seafood, is considered non-toxic.

F. Fourier Transform Infrared Spectrophotometry (FT-IR)

Lack of sensitivity limits the usefulness of this procedure for the screening of solutions except in instances of gross contamination. However, FT-IR may be utilized in conjunction with a microscope for the examination of individual particles or for characterization of substances isolated by physical means. FT-IR can provide identification through matching spectral features with compilations of the IR spectra of reference compounds or it can provide indications of the presence of functional groups to supplement other analytical information.

G. UV-Visible Spectrophotometry (UV-VIS)

With some product types, compare the UV-Visible spectrum of the suspect sample dissolved in a solvent system of ethanol: 0.05M aqueous hydrochloric acid (1:1 v/v) with that of the control sample. A similar method is also applied in which the solvent system is ethanol: 0.05M aqueous sodium hydroxide. In ideal circumstances, these comparisons are capable of revealing the presence of a variety of drugs and other bio-active materials at the mg/l level (15).

However, this technique is most often encountered as an adjunct to modern HPLC instrumentation with photodiode array detectors that can spectrally characterize components during the course of a separation.

14.9 Analytical Documentation

Document the examination and analysis of the complaint/tampering sample on the analyst's worksheet, FDA-431. Information on the analyst's worksheet must include, but is not limited to, chain of custody, all observations, photographic documentation and analytical findings. This information may be used in legal proceedings through the federal courts or local jurisdictions, or in civil procedures through Freedom of Information.

These findings will be reviewed by law enforcement individuals and attorneys who may not have basic knowledge of the science used to determine the findings.

14.10 Reporting

Laboratory management is responsible for communicating results to investigators and/or special agents working on the complaint/tampering incident, as well as the Office of Crisis Management and involved District Compliance Branches, Complaint Coordinators and outside agencies. For reasons addressed in Section 14.9, it is useful to provide a summary of results consisting of

sentences that can be interpreted by law enforcement officials and attorneys outside the Agency. Incorporating key information from the sample collection report in the summary is helpful.

14.11 References

1. U.S. Food & Drug Administration, Office of Regulatory Affairs, (current edition). *Investigations operations manual* (chap. 9, subchap. 900: Complaints).
2. U.S. Food & Drug Administration, Office of Regulatory Affairs, (current edition). *Investigations operations manual* (chap. 9, subchap. 970: Tampering).
3. U.S. Food & Drug Administration, Office of Regulatory Affairs, (current edition). *Investigations operations manual* (chap. 9, Exhibit 970A: Federal Anti-tampering Act).
4. Gosselin, R. E., Smith, R. P., Hodge, H. C. and Braddock, J. E. (1984). *Clinical toxicology of commercial products* (5th ed.). Baltimore: Williams & Wilkins.
5. Bryson, P. D. (1989). *Comprehensive review in toxicology* (2nd ed.). Aspen, CO
6. Safferstein, R. (Ed.). (1982). *Forensic science handbook*. Prentice-Hall
7. Safferstein, R. (Ed.). (1988). *Forensic science handbook* (Vol. II). Prentice-Hall
8. Safferstein, R. (Ed.). (1993). *Forensic science handbook* (Vol. III). Prentice-Hall
9. U.S. Food & Drug Administration, Center for Food Safety and Applied Nutrition, Office of Plant, Dairy Foods and Beverages. Makovi, C. M. (Ed.), McMahon, B. M. (Ed. Emerita). (1994). *Pesticide analytical manual-multiresidue methods* (3rd ed., Vol. I). R.O.W. Sciences, Inc.
10. U.S. Pharmacopeia and National Formulary
11. Horowitz, W. (Ed.). (2000). *AOAC Official Methods of Analysis* (17th ed., Vol. 1 and Vol. 2). Gaithersburg, MD: Association of Official Analytical Chemistry International.
12. Analytical Abstracts, Royal Society of Chemistry on a searchable CD-ROM from Silver Platter International, NV.
13. Hummel, D. O. (2000). *Handbook of surfactant analysis – chemical, physico-chemical and physical methods*. New York: Wiley & Sons.
14. Rosen, M. J. & Goldsmith, H. A. (1972). *Systematic analysis of surface-active agents* (2nd ed.). New York: Wiley-Interscience

15. Moffat, A. C., Jackson, J., Moss, M. S. and Widdup, B. (Eds.). (1986). *Clarke's isolation and identification of drugs* (2nd ed.). London: Pharmaceutical Press.
16. Kolb, B. and Ettre, L. S. (1997). *Static headspace – gas chromatography: theory and practice*. Wiley-VCH.
17. McLafferty, F.W. (2000). *Wiley Registry of Mass Spectral Data*, (7th ed., with NIST Spectral Data). Wiley.
18. U.S. Food & Drug Administration, Center for Food Safety and Applied Nutrition, Office of Plant, Dairy Foods and Beverages. Makovi, C. M. (Ed.), McMahan, B. M. (Ed. Emerita). (1994). *Pesticide analytical manual-multiresidue methods* (3rd ed., Vol. I, chap. 3, sect. 303 Method II for Non-fatty Foods). R.O.W. Sciences, Inc.
19. McLafferty, F. W. and Turecek, F. (1993). *Interpretation of mass spectra* (4th ed.). University Science Books.
20. U.S. Food & Drug Administration, Center for Food Safety and Applied Nutrition. (1984). *Elemental analysis manual* (for foods and related products, 1st Rev.).
21. Laboratory Information Bulletins, FDA, ORA, OO, Office of Regulatory Science.
22. Burke, J. L. and M.S. Ligmond, M. S. The separation and quantitation of butorphanol, nalbuphine, promethazine and methyl paraben found in STANDOL® - a Tampering case. *Laboratory Information Bulletin*, LIB No. 3876.
23. Chase, M. G. (2001, February). Presumptive tests for the presence of bloodstains. *Laboratory Information Bulletin*, LIB No. 4237, 17(2), 1-5.
24. Hill, W. E and Brown, J. R. Screening of containers for foreign objects by the use of diagnostic ultrasound imaging: application in tampering cases. *Laboratory Information Bulletin*, LIB No. 3781.
25. Petzinger, G., Barry, T. L. and J.J. Specchio, J. J., Ph.D. Collision activated dissociation MS- MS analysis of warfarin in Kool-Aid tampering. *Laboratory Information Bulletin*, LIB No. 3168.
26. Holak, W. Cyanide in foods – an overview. *Laboratory Information Bulletin*, LIB No. 3475.
27. Piowar, T. S. Chloramine-T colorimetric determination of trace amounts of cyanide in tea. *Laboratory Information Bulletin*, LIB No. 3029.

28. Mesmer, M. Z. and Flurer, R. A. Determination of bromthalin in commercial rodenticides found in consumer product samples by HPLC/UV-Vis spectrophotometry and HPLC /negative chemical ionization APCI mass spectrometry. *Laboratory Information Bulletin*, LIB No. 4149.
29. McCullough, B. H. series on Cyanide: LIB No. 3026, LIB No. 3027, LIB NO. 3028.
30. Krenitz, B. and Poplawski, T. Screening procedures for cyanide in leaf and instant tea. *Laboratory Information Bulletin*, LIB No. 3107.
31. R. Scroggle, R. Screening Procedures for Cyanide in Samples using the LIXI Fluoroscope. *Laboratory Information Bulletin*, LIB No. 3109.
32. Sinex, S. A., Hight, S. C., Lamont, W. H., Capar, S. G. and Clower, M. G., Jr. Qualitative detection of exogenous cyanide in fruits. *Laboratory Information Bulletin*, LIB No. 3352.
33. Smith, W. T., Meitz, J. L. and Falcone, N. Rapid chloramine-T procedure for the confirmation of cyanide in tested solutions. *Laboratory Information Bulletin*, LIB No. 3358.
34. Daft, J. L. Warfarin poisoning in dog food-assay by HPLC. *Laboratory Information Bulletin*, LIB No. 2256.
35. Heitkemper, D. T, Barnes, B. S., Crowe, J. B., Flurer, C. L., Kaine, L. A., Mulligan, K. J., Sheppard, B. S., Urban, J. R. and Wolnik, K. A. Spot test for the presence of nitrite in spices with confirmation by ion chromatography. *Laboratory Information Bulletin*, LIB No. 3911.

14.12 Document Change History

Version 1.2	Revision	Approved: 09-01-05	Author: LMEB	Approver: LMEB
Version 1.3	Revision	Approved: 02-02-10	Author: LMEB	Approver: LMEB
Version 1.4	Revision	Approved: 02-06-12	Author: LMEB	Approver: LMEB
Version 1.5	Revision	Approved: 02-14-13	Author: LMEB	Approver: LMEB

Version 1.2 changes:

Table of Contents – Section 14.11 added.

Section 14.8 II. – revised fourth paragraph; Section 14.8 III. removed headers A. & B and 1-7 now A-G; revised Section 14.8 III. D. & E.

References formatted with numbers 22. – 35.

Version 1.3 changes:

14.5 – paragraphs 1, 5, and 6 revised

14.8 I. – deleted last sentence

14.8 II. – revised

14.8 III. – paragraphs 1, 2, and 3 revised

14.9 – revised

14.10 - Changed “Division of Emergency Operations” to “Office of Crisis Management”

Version 1.4 changes:

14.3 – deleted “FATA” in second paragraph

14.4 – updated contact information with weblink

14.7 – added “in order” and updated Section 14.4 to 14.5, Safety in third paragraph

14.8 II – deleted supplier name in fourth and fifth paragraph

14.8 III – revised first sentence in first paragraph

14.8 III A. – added (GC_MS) in heading; defined LODs

14.8 III B. – added (GC-MS) in heading; defined FID

14.8 III C. – added (IC) in heading; defined ICP

14.8 III E. – added (ICP-AES) in heading; corrected spelling of Thallium in Table

14.8 III F. – added (FT-IR) in heading

14.8 III G. – added (UV-VIS) in heading

14.9 – deleted second sentence in second paragraph

Version 1.5 changes:

Header – Division of Field Science changed to Office of Regulatory Science

14.11 – Division names removed; ORO change to OO; Division of Field Science changed to Office of Regulatory Science