#### VI. DEVELOPMENT OF THE STANDARD

#### Need for the Standard

The use of pesticides is based on their ability to interfere with basic biochemical processes of living cells and thereby kill the cells or leave them metabolically altered. Numerous examples of adverse effects of all classes of pesticides on individual humans, on worker populations, and on animal systems are detailed in Chapter III. Pesticides have caused diverse toxic effects on various human organs, including the skin, kidneys, eyes, lungs, and reproductive system. pesticides including inorganic arsenic compounds, hexavalent chromium compounds, acrylonitrile, amitrole, benzene, and creosote are probable occupational carcinogens based on data derived from human epidemiologic studies and animal tests. addition. other pesticides are suspected occupational carcinogens, based on data derived from animal experiments. Various pesticides have produced significant neurotoxic, or reproductive effects in animal test systems.

Each year in the United States, occupational exposure to pesticides is directly responsible for many illnesses and injuries. In California alone, during 1975 and 1976, there were 96 reported cases of occupational illnesses resulting from exposure to pesticides in manufacturing and formulating plants [29,297]. Of these, 63 were systemic, 14 involved skin injuries,

17 involved eye injuries, and 2 involved both the skin and the eyes. The cases were the result of exposure to a wide variety of pesticides including mevinphos, captan, diazinon, methomyl, ethylene dibromide, sulfur, methyl bromide, and chlorothalonil.

NIOSH site visits to pesticide manufacturing and formulating plants indicated the need for better control. For example, many plants lacked the capability for medical or industrial hygiene surveillance; employees were often ignorant of the hazards present in their workplace. Skin and respiratory exposures to pesticides, such as prometon during formulation [8(p 14)] and arsenic compounds during production, were observed [8(p 90)]. In addition, the two recent incidents of severe neurotoxic effects in workers exposed to Kepone and leptophos and of reproductive disorders in workers exposed to DBCP emphasize the potential danger to all workers engaged in the manufacture and formulation of pesticides.

#### Relationship to Other Standards

Authority to regulate hazards arising from the manufacture, formulation, distribution, and use of pesticides resides with several Federal agencies and the states. The Occupational Safety and Health Administration (OSHA) has authority for regulating employee exposures arising from pesticides and other chemicals in manufacturing and formulating plants. States are generally responsible for regulating the occupational health of farm workers and applicators within the framework of EPA programs.

Responsibility for administration of the Federal

Insecticide. Fungicide. a nd Rodenticide Act (FIFRA) was transferred to EPA in 1970. FIFRA requires the labeling and registration of pesticides in interstate commerce and the establishment of tolerances for pesticide residues food in The Federal Environmental Pesticide products. Control Act (FEPCA) of 1972 extended the requirements of FIFRA to all pesticides, including those formulated and sold within a state, and contains requirements for establishing a program to certify pesticide applicators for certain restricted pesticides. Pursuant to FEPCA, EPA has established a pesticide reregistration which includes program a rebuttable presumption against registration (RPAR) process. If data, including carcinogenicity, teratogenicity, reproductive effects, ecologic effects, indicate that a pesticide may be harmful to man environment, the Administrator of EPA presumes that the pesticide causes certain effects, and the manufacturer has opportunity to rebut that presumption.

Other Federal agencies having responsibilities with respect to pesticides include the Department of Transportation (DOT), the Federal Trade Commission (FTC), the Food and Drug Administration (FDA), and the Federal Aviation Administration (FAA). DOT, under requirements of the Hazardous Materials Transportation Act, imposes labeling and transportation restrictions on pesticides that are "Class A and B Poisons" (see Table XIV-17). The Federal Aviation Act specifies controls in aerial applications of pesticides. Under this Act, FAA requires certification of aircraft operators before they are permitted to spray. FTC has

proposed a regulation to prohibit pesticide advertisements that claim the product is safer than the label indicates. FDA enforces food tolerances set by the EPA. In summary, the regulatory jurisdictions of agencies other than OSHA include pesticide labeling, registration, setting and tolerances in food products, certification and control exposure of applicators, setting field reentry standards for farmworkers, transportation, and advertising.

Under the Occupational Safety and Health Act of 1970, states may elect to have their own occupational safety and health programs for regulation, provided they meet Federal approval. California has rather comprehensive standards covering pesticide application, including specific rules for fumigation. Medical surveillance, including ChE testing, is required for mixers, formulators, loaders, ground and aerial applicators, and flaggers in the agricultural use of pesticides. California also requires physicians who treat cases of occupational illness or injury to report the cases to the state, which may then investigate the cases in greater detail. However, the state's regulations which relate to workers in pesticide manufacturing and formulating plants are similar to those in 29 CFR 191) as enforced by OSHA.

OSHA has promulgated general requirements that apply to all industries and occupational exposure limits that apply to certain pesticides (see Appendix III). The general standards cover industry in general and are not directed specifically towards pesticide production. Practices such as use of personal protective equipment, sanitation, and fire protection are

contained in the general standards. Exposure limits, developed by the American Conference of Governmental Industrial Hygienists (ACGIH), in terms of 8-hour time-weighted average airborne concentrations, were adopted by OSHA in 1970 for a number of pesticide active ingredients (see Appendix III). OSHA has also developed regulations for two chemicals having minor use as pesticides: benzene and beta propiolactone. NIOSH has developed various criteria documents and recommended standards for limiting exposure to materials registered as pesticides (see Appendix IV). These documents include recommended medical surveillance, work practices, and other elements of a total occupational health standard for protecting workers.

# Form of the Standard

The need for effective protection of workers from hazardous exposures in the manufacturing and formulating of pesticides requires a comprehensive standard. A large number of chemical substances may cause exposure in a variety of operations.

For a single chemical substance, a standard which sets a limit on worker exposure in terms of time and concentration in the workplace air is useful. Such a standard would be particularly appropriate when exposure to the substance through inhalation is the most significant hazard. However, a workplace air concentration limit is useful only if the methods and frequency of monitoring can be specified. The method by which protection from airborne concentrations is achieved must also be part of such a standard and should reflect a preference for

engineering controls over respirator use.

The derivation of environmental (workplace air) limits for pesticide active ingredients and various inerts, 1.500 additives, intermediates, and solvents in pesticide manufacturing and formulating cannot be accomplished as quickly or effectively the design of good work practices and effective engineering The number of materials to be sampled controls. complexities of sampling and analysis in monitoring all pesticides present would be an almost insurmountable task for many formulators. Exposure to nonairborne pesticides as a result of splashes, spills, deposits, and handling is not considered the establishment of an environmental limit. For many pesticides discussed in Chapter III, particularly the organophosphosphorus (OP) compounds, there are significant systemic effects arising from exposure by absorption through skin and other body surfaces. and there are local effects from contact of the chemical with skin, mucous membranes, eyes and their surrounding structures. pesticides, such as dibromochloropropane (DBCP), apparently induce effects at such a low dose that the threshold of effect is at or near the threshold of detection by a reliable analytical technique.

For the production processes used in manufacturing and formulating pesticides, properly engineered equipment provides the best control. The processes are predictable, and controls can be planned and installed to keep pesticides in known limited locations. The costs and effectiveness of engineering controls are predictable and lend themselves to technical evaluation. The

major drawbacks to engineering controls are that they may limit access to processes for observation and control; they require maintenance; and they require a length of time for installation. Engineering controls are desirable as part of a pesticide standard, although variations in processing equipment preclude the development of any standard that specifies the use of particular hardware or systems.

When leaks, spills, or emergencies cause the release o f pesticides into worker-occupied areas, work practices must be relied upon for protection. Work practice controls are necessary, especially to complement engineering controls in situations where the latter give incomplete protection from exposure. Work practice measures also minimize exposure during the cleaning and maintenance of engineering control equipment. They are flexible and can be initiated in a relatively short time The chief weakness of work practices is their reliance on informing and motivating employees to protect themselves. variety of toxic materials handled makes it advantageous to teach general work habits that will protect employees without regard to the types of pesticides they handle. However, the training of employees, as well as all other work practices, should be attuned to the risks present. As discussed in Chapter III, pesticides may affect the body through a variety of exposure routes and cause many different types of effects by a wide range of Because of their diverse toxic actions, pesticides are subjected to different levels of control. Multiple levels of control are designed to allow pesticide manufacturers and formulators to

expend resources on controlling those pesticides that present the greatest risk of adverse toxic effects. The most toxic pesticides require stringent engineering and work practice controls. For those pesticides classified as less toxic, such strict control may be unnecessary.

# Basis for the Recommended Standard

(a) Development of a Classification Scheme

One of the earliest toxicity classifications was developed by Hcdge and Sterner [334], who used the oral LD50 of the substance as the numeric criterion for classification. This approach was modified by Gleason and Hodge [335], who established six toxic categories on the basis of oral LD50 values and assigned designations to these categories. Pesticides with an LD50 less than 5 mg/kg were labeled "super toxic," while those with an LD50 greater than 15,000 mg/kg were labeled "practically nontoxic" (see Table XIV-15). This system is most commonly used to describe the toxicity of a substance and was first employed to quide physicians in the treatment of victims of accidental poisoning by ingestion.

With the passage of FIFRA in 1947. toxicologic classification schemes assumed a new significance. The classification scheme was used to determine the warning words and precautionary statement for the product label.

Until 1970, the US Department of Agriculture (USDA) had the responsibility for administering FIFRA, and set up a toxicity classification scheme to be used in the designation of pesticides

regarded as "highly toxic to man." Pesticides so designated were required to bear the word "Danger" along with the word "Poison" and a skull and crossbones on their labels.

The toxicity classification scheme developed by USDA emphasized the importance of inhalation and dermal exposures in addition to oral intakes and set forth criteria for all three routes of exposure.

In December 1970, EPA was formed and given jurisdiction FIFRA. FIFRA was significantly extended in October 1972 by FEPCA. FEPCA introduced the concept of "restricted use" and "general use" pesticides. Pesticides classified as "restricted" were to be made available only to individuals who were certified as competent in their use, while no such restrictions were placed on users of pesticides classified as "general." In July 1975, EPA promulgated final regulations (40 CFR 162) implementing registration procedures. A classification scheme with toxicity categories was introduced to control labeling, warning, and precautionary statement requirements. This classification scheme was based on oral, inhalational, and dermal toxicity (see Table XIV-16).

Pesticides that are intended for household or other domestic application are classified as "restricted" if they are in toxicity Categories I or II. In making classification decisions, EPA also takes into account whether the pesticide causes any subchronic, chronic, or delayed toxic effects in man under normal conditions of use. A pesticide that causes more than "minor" effects is classified as "restricted."

DOT developed a classification scheme for chemical substances to effect their safe handling during shipment and transportation. The scheme consisted of the dosage criteria below which pesticides were presumed to be toxic to man (see Table XIV-17). Gaseous substances that meet any of the criteria are designated as "Class A Poisons"; solid and liquid substances meeting the criteria are designated as "Class B Poisons." All such substances must be labeled and handled with special precautions during their shipment.

Some nations and international organizations have also developed classification schemes. At a World Health Organization (WHO) conference in 1971, a set of criteria based on rat oral LD50 values was proposed for labeling of pesticide formulations (Table XIV-18). WHO reported that authorities in a number of European countries have adopted these rules and found them both "workable and consistent" [336].

In 1975, WHO recommended a scheme to classify pesticides in order to distinguish between the more and the less hazardous forms of each pesticide [337]. An added feature of this classification method was the inclusion of the physical state of the substance in the criteria. The classification criteria included only dermal and oral exposures. However, the WHO report did point out that if the criteria are applied to solvent-based pesticide formulations, account must be taken of volatility and consequent inhalation toxicity (see Table XIV-19).

Ulanova [338] reported a system of classification of substances according to the level of toxicity that has been

adopted by official agencies of the USSR. The system includes four different class levels, based on toxicity by oral, inhalational, and dermal routes (see Tables XIV-20). Kaloyanova [339] reported a Bulgarian classification scheme, which is similar to the Russian in format, but whose values vary (see Table XIV-21).

Classification schemes based on chronic effects of pesticides are not presently in wide use. OSHA has proposed a system for classifying toxic substances according to evidence of carcinogenicity. The four-category system includes specific types of tests which serve as a basis for classification (Federal Register 42:54148, October 4, 1977).

While there are some differences among the aforementioned systems for classifying pesticides in terms of their acute toxicities, the systems are quite similar, with respect to the oral, inhalational, or dermal toxicity range for very toxic or highly toxic substances.

NIOSH recommends three toxicity categories for the various routes of exposure for defining the hazards of pesticides (see Table VI-1). The recommended classification criteria are very similar to those used by EPA for registration purposes. EFA Categories I and II and NIOSH Groups I and II are identical. NIOSH Group III encompasses both Categories III and IV in the EPA scheme. Listed in Appendix I are approximately 1,500 active ingredients grouped by toxicity. For each pesticide, the most concentrated registered product has been used to determine the resultant group classification because this form is most likely

to be present in manufacturing and formulating workplaces. Registered product data were provided by EPA. In certain cases, seemingly conflicting EPA data indicated that a particular active ingredient had been classified in more than one EPA toxicity class. In those cases, the compound has been grouped in the more stringently controlled NIOSH group. Furthermore, approximately 350 compounds were placed in NIOSH Group III because each not appear as a single concentrated ingredient in any pesticide product. These compounds include certain substances that emulsifiers, detergents, solvents, uses as and other nonpesticidal uses. However, they are registered have biologic activity. ingredients because they It should be stated that there are biologically active emulsifiers, detergents, solvents, and other compounds used in the manufacture and formulation of pesticides that are not EPA-registered active ingredients and therefore do not appear in Appendix I.

TABLE VI-1
DEFINITIONS OF GROUPS I, II, AND III

Hazard Indicators	Texicity Categories		
	I	11	111
Irreversible Effects	Probable or Suspected carcinogenic, neurotoxic, mutagenetic, teratogenetic or reproductive effects		
Ore1 1050	< 50 mg/kg	50-500 mg/kg	> 500 mg/kg
Inhalation LC50	< 0.2 mg/l	0.2-2 mg/l	> 2 mg/l
Dermal LDSG	<200 mg/kg	200-2,000 mg/kg	>2,000 mg/kg
Eye effects	Corrosive; corneal opacity not reversible within 7 d	Corneel opacity reversible within 7 d) irritation persisting for 7 d	No corneal opecity; irritation reversible within 7 d
Skin effects	Corrosive	Severa irritation at 72 hr	Moderate irritation at 72 hr

Pesticides implicated in Chapter III as probable occupational carcinogens or suspected occupational carcinogens, teratogens, neurotoxins, and toxins to the reproductive system are classified in Group I regardless of acute toxicity. The data which these decisions are based are also presented in Chapter III. Various pesticides are currently in the EPA RPAR process, including amitraz, cadmium, diallate, endrin, maleic hydrazide, and pronamide due to suspected carcinogenicity; benomyl, maleic hydrazide, cadmium, and thiophonate-methyl due to suspected mutagenicity; benomyl, cadmium, and ethylene bisdithiocarbamates due to suspected teratogenicity; and benomyl, ethylene dibromide (EDB), maleic hydrazide, hexachlorocylohexane, dimethoate, and lindane due to suspected reproductive effects. EPA's data for these pesticides have not been reviewed by NIOSH; however, once a decision is made concerning reregistration of these compounds, each should be classified in the recommended NIOSH scheme following further review of the EPA data.

Throughout the process leading to the development of this recommended standard, the major emphasis has been on providing protection for workers engaged in the manufacture and formulation of pesticides in the light of necessary time constraints. The recent serious episodes of occupational poisoning due to Kepone and leptophos indicate that effective controls need to be implemented immediately, not several years hence. The relatively long period of time and tremendous expense that would be required for the development of individual recommended standards for all

pesticides mandate that a different approach be taken. A generic industry-wide approach to the development of a recommended standard for the manufacturing and formulating segments of pesticide industry, based primarily on effective engineering controls, work practices, and personal sanitation practices, felt to be the best strategy. Several classification systems that NIOSH was able to find have been examined, and only after their evaluation, was the decision made to adopt a scheme compatible with that used by EPA. Standardization was not main objective, but it is obvious that there is a definite correlation in all classification schemes examined, especially in the areas of extreme or high toxicity. The various systems classification do not differ significantly in terms of their scientific merit. The EPA system is the only other pesticide toxicity rating scheme officially used by the US Government and, since it is in general agreement with those standards recommended by recognized agencies, to devise a different method of classification would result in unnecessary complication. burden on both government and industry will be lessened through the use of uniform criteria.

The basic toxicologic parameter of the recommended classification scheme is the acute lethal dose or concentration. As with any other statistically derived value, variability can be expected in its determination. The variability may be introduced with the number of test animals used, with differences in diet and/or environmental conditions, and with any of a number of factors that affect experimental results. Accordingly, it is

understood that there will be chemicals that seem to bridge two toxicity groupings. Consequently, such pesticides are placed in the group that is more stringently controlled. NICSH recognizes the resultant effect on the classification and regulation of certain pesticides. However, this theoretical disadvantage is more than offset by the facility with which pesticides can be classified under the proposed scheme.

### (b) Medical Surveillance

Preplacement medical examinations should be made available to employees prior to any occupational exposure to pesticides. The purposes of such examinations are the identification of any conditions or disorders predisposing employees to pesticide toxic effects and the assessment of employee ability to use respiratory protective devices. Certain employees should also be counseled by a physician before occupational exposure in those cases where the employees' state of health or parental status poses a peculiar risk to themselves or their children.

Exposure to pesticides has caused a variety of local and systemic health effects. Local effects include chloracne [134,135], erythema [144,145] and other dermal reactions [139-141], and various injuries to the eyes [143]. Organ systems affected b y pesticide exposures are the nervous [37,55], reproductive [118,119], hepatic [121,124], renal [128, 129], hematopoietic [152,154], cardiovascular [161], and respiratory systems [125, 148]. There is also evidence that some pesticides induce cancer in various organs [48,59,167]. Therefore, annual physical examinations are also recommended.

OP pesticides may affect the nervous system by inhibition This effect is cholinesterase (ChE) activity. of reversible by antidotal treatment; however, it slowly is reversible if not treated, and a series of low chronic exposures NIOSH recommends lead to significant ChE depression. (RBC) ChE for all periodic determination of red blood cell workers exposed to OP insecticides. The frequency of determinations should be based on the pesticide(s) to which an employee is exposed, his potential exposure levels, and his state of health. Frequency should be decided by the physician only after he weighs all of these factors and considers the results of previous determinations. RBC ChE may be determined as frequently for certain special circumstances, but no frequently than six times per year which is necessary in order to ensure that changes in the employee's workplace or working habits have not increased his pesticide exposure to unhealthful levels.

# (c) Labeling and Posting

Employees should be apprised of pesticide hazards and methods to protect themselves. Although all employees who will be occupationally exposed to pesticides should already receive such information as part of their training, labels and signs serve as an important reminder. Labels and signs also provide an initial warning to other employees who normally may not deal with pesticides.

### (d) Personal Protective Clothing and Equipment

Protective clothing and equipment protect the pesticide worker from exposure. In pesticide manufacturing and

formulating, employees should cover their body surfaces in order to avoid the local effects of contact with toxic chemicals and also to prevent systemic effects which may arise after absorption of pesticides through body surfaces.

Clothing and equipment should be carefully selected, used, and maintained to be effective. Studies have shown that many materials commonly used in protective equipment are not impermeable to pesticides and solvents [316,317]; however, materials selected for such clothing and equipment should be no more than minimally permeable to the substances involved in employee exposure. Employees must be thoroughly trained to properly use their personal protective clothing and equipment, especially respirators.

Maintenance of protective clothing and equipment includes inspecting, testing, cleaning, and reparing or replacing when necessary. The employer should arrange a system for storing and cleaning equipment and work clothing that guards against the contamination of street clothing or other personal effects of the employees.

#### (e) Informing Employees of Hazards

The toxic effects of pesticides and other chemicals involved in occupational exposure should be fully explained to employees, including probable and potential carcinogenic, teratogenic, mutagenic, neurotoxic, and reproductive effects. In cases where these effects are based on animal data, the risks to man should be explained. Employees should be taught to recognize symptoms of overexposure and to administer first-aid measures in

such cases.

Employee training should fully cover methods to protect workers from chemical exposures in routine work and in emergencies. Written information available to all employees should include toxicity data, first-aid measures, personal protective methods, emergency procedures, and applicable regulations for the substances to which they may be exposed. As plant processes change or new data come to light, employee training and available information should be updated.

# (f) Work Practices

The manner in which employees perform their work should be directed to minimize their exposure. Handling pesticides in contact with skin surfaces should be avoided. Pesticides and other chemicals used in their manufacture and formulation should be kept in appropriate containers and processing equipment; leaks or spills should be promptly cleaned up. Disposal of pesticides and pesticide-contaminated materials should be performed by methods which limit exposure.

Employees should deactivate and decontaminate any equipment before maintenance, in order to prevent injury or exposure. Special precautions should be taken before entering enclosed spaces, especially to protect against respiratory exposure.

#### (g) Sanitation and Personal Hygiene

Employers should provide facilities to allow employees to wash off pesticides and other chemicals. Employees should be advised to cleanse themselves of pesticides to reduce skin exposure and contamination of food or tobacco products which

could lead to oral or respiratory exposure. For that reason, consumption of food, beverage, or tobacco products should be prohibited in areas where pesticides are handled. Sanitation and hygiene practices should be encouraged by employee training, supervision, and the posting of signs.

#### (h) Engineering Controls

To the greatest extent possible, pesticides and other toxic chemicals should be handled within closed systems to minimize employee exposure. Equipment should be designed and situated so that malfunctions do not cause release of chemicals into worker-occupied areas. Regular inspection and maintenance should be conducted to lessen the risk of leaks and malfunctions. Where there is likelihood of escaping pesticides, systems for recapture should be used, ie, exhaust ventilation for airborne pesticides and sumps for liquids.

### (i) Monitoring and Recordkeeping

In order to detect, prevent, and treat employee exposure to pesticides, monitoring with concomitant recordkeeping should be periodically conducted. The effectiveness of engineering controls may be measured by monitoring the workplace atmosphere. The use and success of work practice controls can be assessed by observation of worker functions and by medical surveillance. Records of plant monitoring and employee medical examinations should be compared to detect any correlations between exposure and effect.

The Toxic Substances Control Act of 1976 requires that "Records of...adverse reactions to the health of employees shall

be retained for thirty years from the date such reactions were first reported to or known by the person maintaining such records...." Because medical examinations will often provide the first recognized evidence of an adverse reaction, whether at the time of the examination or retrospectively, it appears consonant with the Toxic Substances Control Act to require medical records on workers engaged in the manufacture or formulation of pesticides to be maintained for 30 years. Furthermore, records of environmental exposures should be kept for the same period, to allow correlation of a worker's exposure with his or her health.

#### VII. RESEARCH NEEDS

There is an obvious need for a wide range of toxicity testing for many of the 1,500 Federally registered pesticides. In a recent notice (Federal Register 41:7218-7375, February 17, 1976), FPA stated that it had reviewed the data in its files on approximately 650 of 1,500 registered active ingredients. Of those reviewed, approximately 470 required further testing before reregistration could begin. Types of tests required included long-term feeding, teratogenicity, mutagenicity, reproductive effects, oncogenicity, and various short-term tests. There is also a need for further studies to elucidate observed behavioral effects in animals and to relate them to humans.

The most important research needs stem from the need or desire for extra care when handling many pesticides. In the area of engineering controls, methods of controlling dusts, vapors, gases, or splashes and spills while performing operations such as packaging or transfer are clearly needed for both manufacturing and formulating. Although for certain operations controls do Improvement of engineering exist, improvements can be made. controls would have a positive impact on the health and safety of employees engaged the manufacture and formulation of in pesticides. Currently, the Control Technology Research Branch of NIOSH is undertaking a study with the purpose of documenting the types of engineering controls now being used in the manufacturing

and formulating industry. The results, to be published in 1979, will document the state of the art with regard to engineering controls and will elucidate those areas where the greatest research and development are needed.

A program should be undertaken to develop more effective satisfactory personal protective clothing and equipment. Emphasis should be placed on developing cool, lightweight, and impervious clothing and equipment. The impermeability, or lack thereof, of various types of protective clothing or equipment, including aprons, gloves, gauntlets, and boots, is an extremely important factor in percutaneous absorbtion of pesticides. permeability varies greatly, depending on the material and the chemical substance. The weave and finish of cloth also affect permeability of clothing. The variations are so great that pesticide manufacturers and formulators should use only protective clothing and equipment that has been tested and found to be highly resistant to penetration of those chemicals of concern.

The decontamination of work clothing requires further research. Though some work has been done involving OC, OP, and carbamate insecticides, there is an obvious need for similar work on other pesticides, including substituted carbamate fungicides, halogenated fumigants, rodenticides, and most herbicides. In the studies done thus far, the results indicate that optimum conditions for decontamination can be estimated, but that in no case has decontamination been complete by the procedures examined.