quantities, by atomizing it in a suitable combustion chamber.

APPENDIX C TO SUBPART C TO PART 197—MEDICAL SURVEILLANCE GUIDELINES FOR BENZENE

I. Route of Entry

Inhalation; skin absorption.

II. Toxicology

Benzene is primarily an inhalation hazard. Systemic absorption may cause depression of the hematopoietic system, pancytopenia, aplastic anemia, and leukemia. Inhalation of high concentrations may affect the functioning of the central nervous system. Aspiration of small amounts of liquid benzene immediately causes pulmonary edema and hemorrhage of pulmonary tissue. There is some absorption through the skin. Absorption may be more rapid in the case of abraded skin or if it is present in a mixture or as a contaminant in solvents which are readily absorbed. The defatting action of benzene may produce primary irritation due to repeated or prolonged contact with the skin. High concentrations are irritating to the eyes and the mucous membranes of the nose and respiratory tract.

III. Signs and Symptoms

Direct skin contact with benzene may cause erythema. Repeated or prolonged contact may result in drying, scaling dermatitis or development of secondary skin infections. In addition, benzene is absorbed through the skin. Local effects of benzene vapor or liquid on the eye are slight. Only at very high concentrations is there any smarting sensation in the eye. Inhalation of high concentrations of benzene may have an initial stimulatory effect on the central nervous system characterized by exhilaration, nervous excitation, or giddiness, followed by a period of depression, drowsiness, or fatigue. A sensation of tightness in the chest accompanied by breathlessness may occur and ultimately the victim may lose consciousness. Tremors, convulsions, and death may follow from respiratory paralysis or circulatory collapse in a few minutes to several hours following severe exposures.

The detrimental effect on the blood-forming system of prolonged exposure to small quantities of benzene vapor is of extreme importance. The hematopoietic system is the chief target for benzene's toxic effects which are manifested by alterations in the levels of formed elements in the peripheral blood. These effects may occur at concentrations of benzene which may not cause irritation of mucous membranes or any unpleasant sensory effects. Early signs and symptoms of benzene morbidity are varied. Often, they are not readily noticed and are non-specific. Complaints of headache, dizziness, and loss of appetite may precede or follow clinical signs. Rapid pulse and low blood pressure, in addition to a physical appearance of anemia, may accompany a complaint of shortness of breath and excessive tiredness. Bleeding from the nose, gums, or mucous membranes and the development of purpuric spots (small bruises) may occur as the condition progresses. Clinical evidence of leukopenia, anemia, and thrombocytopenia, singly or in combination, may be among the first signs.

Bone marrow may appear normal, aplastic, or hyperplastic and may not, in all situations, correlate with peripheral blood forming tissues. Because of variations in the susceptibility to benzene morbidity, there is no ''typical'' blood picture. The onset of effects of prolonged benzene exposure may be delayed for many months or years after the actual exposure has ceased. Identification or correlation with benzene exposure must be sought out in the occupational history.

IV. Treatment of Acute Toxic Effects

Remove from exposure immediately. Make sure you are adequately protected and do not risk being overcome by fumes. Give oxygen or artificial resuscitation, if indicated. Flush eyes, wash skin if contaminated, and remove all contaminated clothing. Symptoms of intoxication may persist following severe exposures. Recovery from mild exposures is usually rapid and complete.

V. Surveillance and Preventive Considerations

(a) *General.* The principal effects of benzene exposure addressed in 46 CFR part 197, subpart C, appendix A, are pathological changes in the hematopoietic system, reflected by changes in the peripheral blood and manifested clinically as pancytopenia, aplastic anemia, or leukemia. Consequently, the medical surveillance program specified in 46 CFR 197.560 is designed to observe, on a regular basis, blood indices for early signs of these effects. Although early signs of leukemia are not usually available, emerging diagnostic technology and innovative regimes are making consistent surveillance for leukemia, as well as other hematopoietic effects, more and more beneficial.

Initial and periodic medical examinations must be provided as required in 46 CFR 197.560. There are special provisions for medical tests in the event of hematologic abnormalities or emergencies.

The blood values which require referral to a hematologist or internist are noted in 46 CFR 197.560(d) (i), (ii), and (iii). That section specifies that, if blood abnormalities persist, the employee must be referred unless the physician has good reason to believe that the referral is unnecessary. Examples of conditions that might make a referral unnecessary despite abnormal blood limits are iron

or folate deficiency, menorrhagia, or blood loss due to some unrelated medical abnormality.

Symptoms and signs of benzene toxicity can be non-specific. Only a detailed history and appropriate investigative procedures will enable a physician to rule out or confirm conditions that place the employee at increased risk. To assist the examining physician with regard to which laboratory tests are necessary and when to refer an employee to the specialist, the following guidelines have been established.

(b) *Hematology Guidelines.* A minimum battery of tests is to be performed by strictly standardized methods.

(1) Red cell, white cell, platelet counts, white blood cell differential, hematocrit, and red cell indices must be performed by an accredited laboratory. The normal ranges for the red cell and white cell counts are influenced by altitude, race, and sex and, therefore, should be determined by an accredited laboratory in the specific area where the tests are performed.

Either a decline from an absolute normal or from an individual's base line to a subnormal value or a rise to a supra-normal value are indicative of potential toxicity, particularly if all blood parameters decline. The normal total white blood count is approximately 7,200/mm^3 plus or minus 3,000. For cigarette smokers, the white count may be higher and the upper range may be 2,000 cells higher than normal for the laboratory. In addition, infection, allergies, and some drugs may raise the white cell count. The normal platelet count is approximately 250,000 with a range of 140,000 to 400,000. Counts outside this range should be regarded as possible evidence of benzene toxicity.

Certain abnormalities found through routine screening are of greater significance in the benzene-exposed worker and require prompt consultation with a specialist, namely:

(i) Thrombocytopenia.

(ii) A trend of decreasing white cell, red cell, or platelet indices in an individual over time is more worrisome than an isolated abnormal finding at one test time. The importance of a trend highlights the need to compare an individual's test results to baseline, to previous periodic tests, or to both.

(iii) A constellation or pattern of abnormalities in the different blood indices is of more significance than a single abnormality. A low white count not associated with any abnormalities in other cell indices may be a normal statistical variation. Whereas, if the low white count is accompanied by decreases in the platelet and/or red cell indices, such a pattern is more likely to be associated with benzene toxicity and merits thorough investigation.

Anemia, leukopenia, macrocytosis, or an abnormal differential white blood cell count should alert the physician to investigate further and to refer the patient if repeat tests confirm the abnormalities. If routine screening detects an abnormality, the follow-up tests which may be helpful in establishing the etiology of the abnormality are the peripheral blood smear and the reticulocyte count.

The extreme range of normal for reticulocytes is 0.4 to 2.5 percent of the red cells. The usual range is 0.5 to 1.2 percent of the red cells. A decline in reticulocytes to levels of less than 0.4 percent is to be regarded as possible evidence of benzene toxicity requiring accelerated surveillance (unless another specific cause is found). An increase in reticulocyte levels to above 2.5 percent also may be consistent with, but not characteristic of, benzene toxicity.

(2) A careful examination of the peripheral blood smear is an important diagnostic test. As with the reticulocyte count, the smear should be with fresh uncoagulated blood obtained from a needle tip following venipuncture or from a drop of earlobe blood (capillary blood). If necessary, the smear may, under certain limited conditions, be made from a blood sample anticoagulated with EDTA (but never with oxalate or heparin). When the smear is to be prepared from a specimen of venous blood which has been collected by a commercial Vacutainer® type tube containing neutral EDTA, the smear should be made as soon as possible after the venesection. A delay of up to 12 hours is permissible between the drawing of the blood specimen into EDTA and the preparation of the smear if the blood is stored at refrigerator (not freezing) temperature.

(3) The minimum mandatory observations to be made from the smear are as follows:

(i) The differential white blood cell count.

(ii) Description of abnormalities in the appearance of red cells.

(iii) Description of any abnormalities in the platelets.

(iv) A careful search must be made of every blood smear for immature white cells such as band forms (in more than normal proportion, *i.e.*, over ten percent of the total differential count), any number of metamyelocytes, myelocytes, or myeloblasts. Any nucleate or multinucleated red blood cells should be reported. Large ''giant'' platelets or fragments of megakaryocytes must be recognized.

An increase in the proportion of band forms among the neutrophilic granulocytes is an abnormality deserving special mention. Such an increase may represent a change which should be considered as an early warning of benzene toxicity in the absence of other causative factors (most commonly infection). Likewise, the appearance of metamyelocytes, in the absence of another probable cause, is to be considered a possible indication of benzene-induced toxicity.

An upward trend in the number of basophils, which normally do not exceed about 2.0 percent of the total white cells, is to be regarded as possible evidence of benzene toxicity. A rise in the eosinophil count is less specific but may indicate toxicity if the rise is above 6.0 percent of the total white count.

The normal range of monocytes is from 2.0 to 8.0 percent of the total white count with an average of about 5.0 percent. About 20 percent of individuals reported to have mild but persisting abnormalities caused by exposure to benzene show a persistent monocytosis. The findings of a monocyte count which persists at more than ten to 12 percent of the normal white cell count (when the total count is normal) or persistence of an absolute monocyte count in excess of 800/mm^3 should be regarded as a possible sign of benzene-induced toxicity.

A less frequent but more serious indication of benzene toxicity is the finding in the peripheral blood of the so-called ''pseudo'' (or acquired) Pelger-Huet anomaly. In this anomaly, many, or sometimes the majority, of the neutrophilic granulocytes possess two round nuclear segments, or, less often, one or three round segments, rather than three normally elongated segments. When this anomaly is not hereditary, it is often, but not invariably, predictive of subsequent leukemia. However, only about two percent of patients who ultimately develop acute myelogenous leukemia show the acquired Pelger-Huet anomaly. Other tests that can be administered to investigate blood abnormalities are discussed below. However, these tests should be undertaken by the hematologist.

An uncommon sign, which cannot be detected from the smear but can be elicited by a ''sucrose water test'' of peripheral blood, is transient paroxysmal nocturnal hemoglobinuria (PNH). This sign may first occur insidiously during a period of established aplastic anemia and may be followed within one to a few years by the appearance of rapidly fatal, acute myelogenous leukemia. Clinical detection of PNH, which occurs in only one or two percent of those destined to have acute myelogenous leukemia, may be difficult. If the ''sucrose water test'' is positive, the somewhat more definitive Ham test, also known as the acid-serum hemolysis test, may provide confirmation.

(v) Individuals documented to have developed acute myelogenous leukemia years after initial exposure to benzene may have progressed through a preliminary phase of hematologic abnormality. In some instances, pancytopenia (*i.e.*, a lowering in the counts of all circulating blood cells of bone marrow origin, but not to the extent implied by the term ''aplastic anemia'') preceded leukemia for many years. Depression of a single blood cell type or platelets may represent a harbinger of aplasia or leukemia. The finding of two or more cytopenias or pancytopenia in a benzene-exposed individual must be regarded as highly suspicious of more advanced, although still reversible, toxicity. Pancytopenia coupled with the appearance of immature cells (myelocytes, myeloblasts, erythroblasts, etc.) with abnormal cells (pseudo Pelger-Huet anomaly, atypical nuclear heterochromatin, etc.) or of unexplained elevations of white blood cells must be regarded as evidence of benzene overexposure, unless proved otherwise. Many severely aplastic patients manifested the ominous finding of five to ten percent myeloblasts in the marrow, occasional myeloblasts and myelocytes in the blood, and 20 to 30 percent monocytes. It is evident that isolated cytopenias, pancytopenias, and even aplastic anemias induced by benzene may be reversible and complete recovery has been reported on cessation of exposure. However, because any of these abnormalities is serious, the employee must immediately be removed from any possible exposure to benzene vapor. Certain tests may substantiate the employee's prospects for progression or regression. One such test would be an examination of the bone marrow, but the decision to perform a bone marrow aspiration or needle biopsy must be made by the hematologist.

The findings of basophilic stippling in circulating red blood cells (usually found in one to five percent of red cells following marrow injury) and detection in the bone marrow of what are termed ''ringed sideroblasts'' must be taken seriously, as they have been noted in recent years to be premonitory signs of subsequent leukemia.

Recently peroxidase-staining of circulating or marrow neutrophil granulocytes, employing benzidine dihydrochloride, have revealed the disappearance of, or diminution in, peroxidase in a sizable proportion of the granulocytes. This has been reported as an early sign of leukemia. However, relatively few patients have been studied to date. Granulocyte granules are normally strongly peroxidase positive. A steady decline in leukocyte alkaline phosphatase has also been reported as suggestive of early acute leukemia. Exposure to benzene may cause an early rise in serum iron, often but not always associated with a fall in the reticulocyte count. Thus, serial measurements of serum iron levels may provide a means of determining whether or not there is a trend representing sustained suppression of erythropoiesis.

Measurement of serum iron and determination of peroxidase and of alkaline phosphatase activity in peripheral granulocytes can be performed in most pathology laboratories. Peroxidase and alkaline phosphatase staining are usually undertaken when the index of suspicion for leukemia is high.