

# Effectiveness of Federally Required Medical Laboratory Screening in the Detection of Chemical Liver Injury

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The increasing concern of industrialized societies over the potential health hazard of synthetic chemicals in the occupational environment has led to government requirements for medical laboratory screening of workers. The specific tests for such screening programs are most often selected on the basis of medical experience which utilized them in symptomatic or hospitalized populations. Required screening tests for hepatic injury including cancer in vinyl chloride workers has been systematically and prospectively studied in an industrial population working with synthetic rubber and plastics. Approximately 1300 employees were studied over a five-year period. A cohort of 969 male employees, for the purposes of analysis, were divided into a "standard" and "nonstandard" population based upon the absence or presence of significant medical disease (including liver disease). A subcohort of 120 individuals was further identified based on availability of liver biopsy. Evaluation of federally required studies included alkaline phosphatase (AP),  $\gamma$ -glutamyl transpeptidase (GGT), alanine aminotransferase (ALT, SGPT), aspartate aminotransferase (AST, SGOT) and bilirubin (BR). Also studied were indocyanine green clearance (ICG) and radioisotopic liver spleen scans (L-S scans). The GGT provided the highest positive predicted value as a screening test for identifying "nonstandard" individuals (individuals with all types of medical disease) followed by ICG, AST, ALT, L-S scan, AP, and BR.

In the identification of asymptomatic liver disease the GGT had the least specificity due to a high false positive rate, while the AP provided the highest specificity. The ICG clearance however, provided the best combination of positive predictive value and sum of specificity and sensitivity. The AP provided additional increase in specificity as a follow-up study. There was no evidence that any of the other federally required tests added any additional benefit and did add significant increase in the false positive rate. These studies support the need for evaluating screening tests as to their sensitivity, specificity and positive predictive value, in asymptomatic individuals, before they are made established requirements.

## Introduction

Industrialized societies throughout the world have become increasingly concerned over the potential health hazard of synthetic chemicals in the occupational environment. Governmental regulations have increased the number and types of medical laboratory screening required for a large variety of halogenated hydrocarbons as well as other potential environmental hazards. The primary objective of these screening programs is to

reduce disability, morbidity and mortality in workers, especially as related to serious low-grade health hazards. In general, screening programs are instituted because of the presence in the work environment of a suspected or proven environmental toxin or carcinogen, which has the potential of producing low-grade injury over long periods of exposure.

Most screening studies are directed toward the detection of abnormalities in certain body systems. The specific tests are frequently selected on the basis of medical experience which utilized them in symptomatic or hospitalized populations. Prior experiences utilizing nonspecific multiphasic health surveillance screening and maintenance have not proven to be cost effective except under certain limited

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conditions (1). The cost effectiveness of such tests, however, in the determination of medical screening requirements, has played a limited role due to the potential seriousness of these occupational agents. Little attention has been paid as to whether the effectiveness of federally required screening provides the best or, more importantly, a necessary benefit when applied to asymptomatic and otherwise healthy worker populations.

The discovery in 1974 of hepatic toxicity and cancer formation in vinyl chloride workers provided the opportunity to systematically and prospectively study the effectiveness of federally required and federally recommended medical screening procedures for the detection of chemical liver injury, including cancer development (2). Table 1 lists the federally required medical screening procedures since 1974 for environments utilizing vinyl chloride or polyvinyl chloride. Table 2 lists the federally recommended studies for these same environments. This paper will present a preliminary assessment of the effectiveness of these federally required studies in the accurate detection and identification of chemically induced liver injury due to halogenated hydrocarbons, especially vinyl chloride.

## Materials and Methods

The industrial population studied consisted of approximately 1200-1400 employees of a chemical plant whose two major products were synthetic rubber and plastics. The industrial plant had been in operation for over 35 years and had a predominance of male employees (96%), approximately 80-87% of the work force being white, 11-12% black, less than 1% of other racial origins. Turnover of the plant was approximately 10 to 15% per year with 65-70% of the work force having worked five years or more at the plant. Employee ages ranged from 18-65, with a mean of 52 years.

A cohort consisting of 969 male employees who worked continually from June 1, 1976 to May 31, 1977 was, for purposes of this analysis, divided into a "standard" and a "nonstandard" population. These designations were given on the basis of a review of

Table 1. Federally required studies for vinyl chloride workers.

|                                                  |
|--------------------------------------------------|
| History and physical                             |
| < 10 years as vinyl chloride worker—(annual)     |
| > 10 years as vinyl chloride worker—(semiannual) |
| Biochemical studies                              |
| SGOT (AST)                                       |
| SGPT (ALT)                                       |
| GGTP                                             |
| AP                                               |
| TB                                               |

Table 2. Federally recommended (not required) studies.

|                                        |
|----------------------------------------|
| Hepatic studies                        |
| LDH isoenzyme                          |
| Total protein                          |
| Protein electrophoresis                |
| Hb <sub>A<sub>1c</sub></sub>           |
| Radioisotopic scan                     |
| Kidney dysfunction (urine examination) |
| Albumin                                |
| RBC                                    |
| Exfoliative abnormal cells             |
| Pulmonary system                       |
| FVC                                    |
| FEV <sub>1</sub>                       |
| Chest x-ray (PA and lateral)           |

all present standard medical data on each employee, including the federally required studies. Other screening studies of the medical surveillance programs were not utilized in the classification of overall medical status because, at that time, their clinical usefulness was unknown or controversial. All studies were performed on an annual basis; those individuals with ten years or more of employment were examined and screened semiannually. Compliance with medical screening studies during the five-year study period showed a continuous participation in the history and physical examinations by over 75% of the work force, laboratory tests and chest x-rays by 86%, and liver-spleen scans by 85%. Seventeen percent failed to undergo at least one history and physical examination, 9% did not have any of the radiological studies, and only 4% failed to have laboratory studies during this period. Approximately 40-50% of these individuals who did not undergo an examination claimed to have been examined by their private physician.

A subcohort of 120 individuals was further identified based on the availability of a liver biopsy performed for medical reasons, both related and not related to their work.

The term "standard" is used for those individuals who, based upon the best medical opinion, demonstrated no evidence of any significant medical disease, occupational or nonoccupational in origin. The "nonstandard" population included all others not included in the standard population.

The subcohort population was divided into those individuals with and without histological evidence of liver injury and further subdivided into those with and without histological features characteristic of chemical injury.

All employees had individual work histories. These consisted of a standardized job classification for all jobs within the plant since its opening and a

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rank ordering of exposure for 22 different suspected or potentially hazardous hepatotoxic chemicals used within the work place (3-5). The agents were rank ordered on the basis of the intensity of exposure for each of the job classifications for each of the years that the plant was in operation. From this detailed work history, a cumulative exposure ran month ration (CERM) was determined for each employee for each of the 22 chemicals. All histological material was classified as to the presence or absence of liver disease, and to whether the abnormalities were consistent with chemical or non-chemical injury. This classification was conducted double blindly by three experienced physicians, two pathologists, and a hepatologist (6), without knowledge of any medical data, exposure or work history.

## Results

Although 50 or more biochemical screening tests were performed during this study period, this paper will limit itself to the evaluation of the federally required studies, the indocyanine green clearance (ICG) study at the 0.5 mg/kg dose (7, 8) and radioisotopic liver and spleen scan (9). The

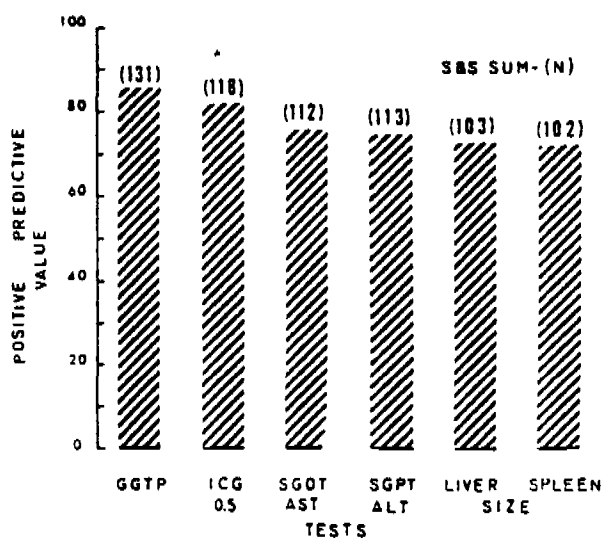


FIGURE 1. Positive predictive values of screening tests in identification of medical disease in an asymptomatic working population ( $N = 969$ ). All those screening tests with positive predictive values of greater than 70 are shown except for indirect bilirubin (due to high number of congenital indirect hyperbilirubinemia) and triglyceride determination. Above each bar in the graph are shown the sum values for sensitivity and specificity of each test. They generally follow the same ranking.

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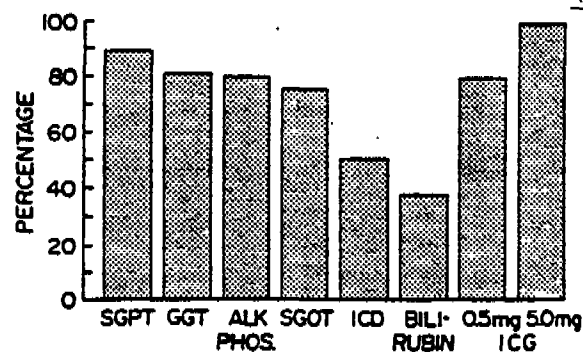


FIGURE 2. Frequency with which clinical biochemical tests correctly reflex the presence of hepatic damage in chemical workers suspected of having liver disease: (SGPT) alanine aminotransferase (ALT) (GGT)  $\gamma$ -glutamyl transpeptidase, (SGOT) aspartic aminotransferase (AST), (Alk. Phos.) alkaline phosphatase, (ICD) isocitric dehydrogenase (ICG) Indocyanine Green clearances at 0.5 and 5.0 mg/kg dose.

federally required biochemical studies include alkaline phosphatase (AP),  $\gamma$ -glutamyl transpeptidase (GGTP), alanine aminotransferase (ALT/SGPT), bilirubin (ALT/SGPT), and the aspartic aminotransferase (AST/SGOT).

The positive predictive values of these screening tests in identifying medical disease (including liver disease) in this asymptomatic working population are shown in Figure 1. The GGTP provided the highest positive predictive value as a screening test for "nonstandard" individuals. It also provided the highest sensitivity and specificity sum shown in brackets. The predictive value of the other tests, in decreasing positivity were ICG, AST, ALT, liver and spleen scan, AP, and bilirubin.

Further evaluations were conducted on the subcohort population in whom we had both histological and biochemical data concerning hepatocellular damage. If one looks at only those individuals who received liver biopsies for suspected liver disease then one would find the percent of positive tests as illustrated in Figure 2. The ALT (SGPT), GGTP, AP and AST (SGOT) demonstrate a very high degree of sensitivity in identifying individuals with hepatic disease. As shown on the right, ICG clearances at the 0.5 mg/kg level provide a similar degree of sensitivity to SGOT and AP. The higher dose ICG clearance (5 mg/kg) appears to provide the most sensitivity for latent hepatic disease. These findings are consistent with the general medical experience with hospitalized patients.

Sensitivity alone however is not an adequate indicator of a test's screening value, especially when used in asymptomatic individuals. More appropriate evaluation of these tests' value as screening instruments are shown by their sensitivity, specificity

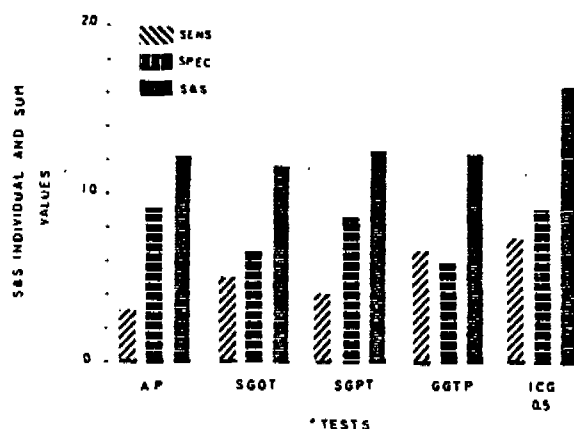


FIGURE 3. Sensitivity and specificity of various biochemical screening tests and their sensitivity and specificity sum values (S & S) based on 78 with biopsy documentation of their hepatic status and all of the biochemical screening studies listed. All screening tests with S & S sums less than 110 (e.g. bilirubin and isocitric dehydrogenase, are not illustrated).

and sum values shown in Figure 3 in the biopsied subpopulation. Here again,  $\gamma$ -glutamyl transpeptidase and ICG clearance (0.5 mg dose) show the greatest sensitivity for identifying individuals with liver disease. However, GGTP had the least specificity, reflecting its high incidence of false positives. Specificity increased with the use of AST, ALT, and ICG clearance. The alkaline phosphatase provided the highest specificity, suggesting that mild or low grade chronic hepatic injury due to environmental agents may be activating hepatic AP synthesis in the absence of biliary tract obstruction or cholestasis. The ICG clearances, even at the low dose (0.5 mg/kg), clearly remains the test with the best combined sensitive and specific screening study for detection of individuals with subclinical hepatic disease.

This subcohort biopsied group was further examined on the basis of the histological interpretation of their liver biopsies and their work exposure to vinyl chloride. All biopsied individuals were subdivided into three groups: 19 with histological evidence consistent with chemical liver injury; 30 with histological evidence of liver disease, nonchemical liver injury; and 29 with normal liver biopsies. Each of the histological subgroups were further subdivided based on their vinyl chloride exposure, on a scale of 1 to 4 (Fig. 4).

The chemical liver injury group contained the highest percentage of individuals with the highest average rating (CERM) for vinyl chloride exposure. In contrast, with those with liver disease, nonchemical, and those with normal livers have a

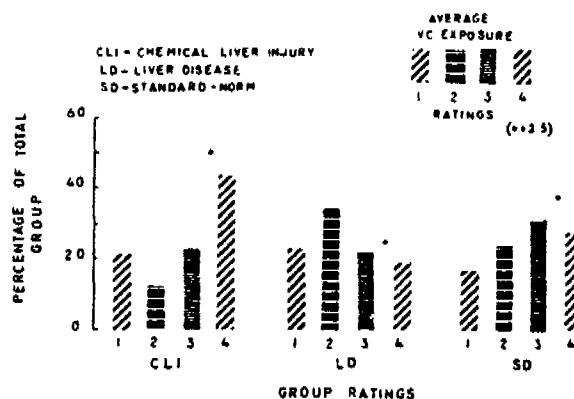


FIGURE 4. Correlation between the histologic findings on liver biopsy and each individual's average total vinyl chloride exposure based on their average CERM (Cumulative Exposure Rank Months) ratings. Rankings: 1 = lowest possible exposure; 2 = minimal exposure, low levels; 3 = moderate exposure; 4 = worked in areas subject to occasional high excursions, or frequently high and/or had intimate contact.

more even distribution of individuals relative to their degrees of vinyl chloride exposure.

In our previous studies we noted that almost all individuals with histologically specific lesion of vinyl chloride injury or angiosarcoma had a total average CERM rating of 3.5 or greater. The asterisk in Figure 3 indicates the percentage of individuals in each of the three histological groups with exposure ratings of 3.5 or greater. Again, the chemical liver injury group have the highest percentage of individuals with the high exposure ratings. This further supports previous work (4, 10) identifying focal hepatocellular hyperplasia as the earliest histological characteristics of chemical injury in liver disease.

A study of the frequency with which these tests are positive among those individuals with liver disease, based on their histological findings (chemical versus nonchemical), provides additional data supporting the clinical observation that an increased AP has a greater specificity for chronic liver injury.

Figure 5 shows the ratio of the proportion of positive screening tests in those with histological chemical liver disease divided by the proportion of positive tests in those whose disease is not of chemical origin. All tests, independent of their sensitivity and specificity for liver injury, were more frequently abnormal in the presence of nonchemical, subclinical liver injury, except for AP. In contrast, AP was far more frequently abnormal in those individuals with chemical liver injury, which tended to be more chronic than acute and generally less severe.

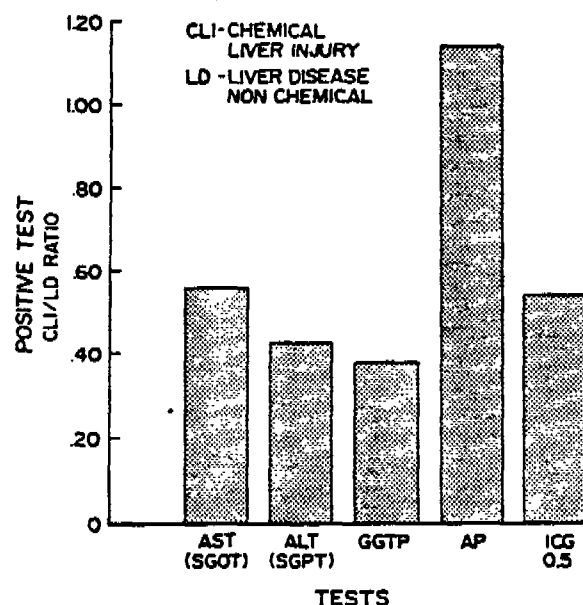


FIGURE 5. Frequency with which biochemical tests were abnormal in those with different type of hepatic injury expressed as a ratio: (CLI) chemical liver injury, (LD) liver disease, nonchemical.

## Discussion

This preliminary systematic review of the positive predictive values and the sensitivity and specificity of federally and some non-federally required tests for chemical workers provides the first scientific and biological basis for the selection of medical screening tests for liver injury in occupational environments. Although these commonly used medical tests have been found by clinical experience to be effective as diagnostic tools in the symptomatically ill or hospitalized population, little clinical work has been done to determine their ability to accurately separate biological variations from early latent or underlying disease in asymptomatic individuals. Tests which provide very high false-positive rates (decreased specificity) such as GGTP, interfere with the screening process identification of the high risk worker by the extra time and cost required for repeat testing, the decreased productivity for the employer, the employees' increased anxiety, and by the loss of confidence in the effectiveness of the testing program by both employees and employer. Determination of the sensitivity and specificity of screening studies for asymptomatic individuals is essential if effective recommendations are to be made a federal requirement. This evaluation process also provided the

best means of developing effective triage protocols for the screening program. For example, in this particular population of industrial workers, we have shown that the assessment of hepatic function is best accomplished by low dose ICG clearance (0.5 mg/kg). The ICG clearance is somewhat a more complicated technique (i.e., injection of substance and repeated blood sampling) but requires only 10 min to perform, and needs only one needle stick. In exchange it provides the best singular screening test for latent hepatic injury. If adequate medical facilities are not easily accessible, then ALT should be substituted. If either ICG clearance and/or ALT studies are found to be abnormal, an AP should be done and a diagnostic work-up instituted to determine the etiology (11).

The rationale for these recommendations is based on the actual study of chronic subacute chemical injury in an asymptomatic population, not preselected because of signs or symptoms. Therefore the test's ability to correctly differentiate disease from nondisease or one type of injury from another is more accurately determined. Chemical and environmental agents of low toxicity tend to produce repeated or persistent injury which accumulates over time. Tests which measure overall functional capacity quantitatively or semiquantitatively, rather than measuring acute low-grade injury over time are more likely to detect changes. For this reason, clearance or tolerance studies provide the best means for identifying latent hepatic disease, while enzyme studies like ALT, GGTP, and SGOT usually reflect acute cellular injury of higher grade or degree and cannot accurately reflex accumulative damage until very late in the disease process. Tests which provide information concerning the progression or nonprogression of injury will be far more helpful to the practicing occupational physician. They provide him/her with a better capability to discern between nonoccupational and occupational disease, and the best available reassurance for the worker of his or her safety while allowing the greatest possibility for continued productivity and employment.

Finally, these data provide a sound scientific basis upon which to modify federal requirements. The removal of specific testing requirements which, with field experience, prove not to have any significant positive predictive value, or effective sensitivity and specificity will aid in reducing overall cost and help maintain continued compliance by industry and workers. There may be theoretical reasons to maintain or continue some of the present federally required screening studies, but these reasons should be separately identified and not be confused with the purposes of the more effective test in the

detection of occupationally related liver injury.

The capabilities and limitations of any new tests or old tests for new screening purposes in detection of other potential occupational hazards, should be validated before making them a required screening procedure. This would lay the foundation for systematic determination of effectiveness of screening procedure against a proven standard. Unvalidated federal requirements provide the worker and employer with a false sense of security and safety by what is believed to be effective monitoring. More importantly, such a situation can lead to delay in effective correction of cause and disease prevention.

## Conclusions

Biochemical screening for hepatic injury in asymptomatic chemical workers can be done most effectively by the use of liver specific clearance studies. ICG clearance provides the best combination of positive predictive value and sensitivity and specificity for functional hepatic testing at the present time.

None of the present federally required studies provide any significant degree of sensitivity without marked reduction in specificity in asymptomatic individuals.

The ALT (SGOT) is the most useful among those Federal tests presently required and the alkaline phosphatase may provide additional specificity as a follow-up study in those individuals with positive ICG or ALT screening studies.

There is no evidence that any of the other federal studies add any benefit and strong evidence that they significantly increase the false-positive results in well individuals.

All screening studies should undergo evaluation as to their positive predictive value and sensitivity and specificity in asymptomatic individuals before becoming permanent or established requirements.

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