# Chromosome Studies in Workers Exposed to Benzene or Toluene or Both

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Chromosome studies were carried out on peripheral blood lymphocytes of 34 workers of a benzene plant, and in 34 controls matched for sex and age. Ten of the workers were exposed to benzene before 1953 and then to toluene, and the others have been exposed only to toluene after 1953. The proportions of unstable and stable chromosome aberrations were significantly higher statistically in the benzene group compared with the controls, and in the benzene group in comparison with the toluene group. No significant differences were found between the frequencies of chromosome changes in the toluene and control groups.

CHRONIC inhalation of benzene vapors is known to be able to induce toxic effects on the bone marrow, resulting in pancytopenias, which can eventually evolve into leukemias.[1,2] The cytotoxic effect of benzene however does not seem to be restricted to bone marrow cells, but also involves other cell types. Several recent reports have appeared which chromosome aberrations were induced by occupational exposure to benzene not only in bone marrow cells,[3-5] but also in the lymphocytes of peripheral blood. The increased rate of chromosome changes in lymphocytes *cultured* in vitro was demonstrated not only in subjects with benzene pathy,[4,6] but in subjects recovered from benzene hemopathy,[4] and in subjects exposed to benzene without overt signs of blood

The chromosome aberrations observed are specific, similar to those induced by x-rays, and can persist even several years after cessation of exposure. They may, therefore, represent a sign of cellular damage caused by the toxic agent, provided the exposure to other *chemical* or physical agents capable of inducing chromosome changes is ruled out.

In 1952 to 1953 an epidemic of benzene-poisoning occurred in a rotogravure plant, where benzene was largely used as an ink solvent and diluent. Many workers suffered from severe benzene hemopathy, many showed slight hematologic changes, and only a few showed no sign of toxicity.[3] Since then toluene (containing traces of xylene) was substituted completely for benzene.

The present investigation, part of a wider study on chromosomal damage from benzene, was *carried* out to study the frequencies of chromosome aberrations among workers of the Same rotogravure plant, some of whom had had known exposure to benzene before 1953 and to toluene after that time, but most of whom have been exposed only to toluene. The rates were compared with those observed in a group of matched controls.

## Materials and Methods

The subjects studied in this survey were 39 male workers, who had been occupationally exposed to benzene, or its homologues (toluene with traces of xylene), or both in a rotogravure

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plant. Their blood status has been checked every three months since 1953.

The chromosome studies were performed in 1967 and 1968. They were carried out blindly by two of us (A.F. and E.P.). Only after completion of the study the exposure and hematologic data as well as the history of the workers were collected by one of us (A.L.). After collection of the data, two subjects were discarded from the final evaluation due to therapeutic exposure to x-rays for ankylosing spondylitis, and three were discarded due to occupational exposure to other chemicals like lead, suspected of inducing chromosome changes. The exposure data are reported in Tables 1 and 2, together with the results of the chromosome studies and some hematologic notes.

At the time of the cytogenetic study, each worker was matched with a healthy control from the general population, of the same sex and approximately the same age (within ± 4 years), with no history of exposure to benzene or its homologues, or to therapeutic or occupational x-irradiation. We could not exclude subjects with exposure to diagnostic x-irradiation, especially of the chest, due to the high frequency of this diagnostic procedure, but it must be remembered that the subjects under study also had occasionally had diagnostic x-rays. For both subjects and controls, we tried to rule out recent viral diseases (especially hepatitis) and recent vaccinations, in both of which conditions rates of chromosome aberrations higher than usual are described.

The chromosome studies were performed on peripheral blood lymphocytes cultured in vitro for 68 to 70 hours with phytohemagglutinin, according to minor modifications of the method of Moorhead et al.[10] The 68 to 70 hours culture period was chosen instead of a shorter time, as suggested by Buckton and Pike,[11] since no significant differences in chromosome aberration yields were found, and a larger number of mitoses was available for scoring.

In most cases 100 metaphases from each subject or control were counted and scored for chromosome aberrations. Counts were performed directly under the microscope at × 1,250. Metaphases with dubious chromosome aberrations and some apparently normal ones were photographed and karyotyped. At the direct analysis of the single metaphases, an evaluation was made of the chromosomes belonging to easily recognizable groups, such as A, D, G, and Y. Each metaphase was classified according to Buckton et al[3] as: A, cells with apparently normal chromosome complement; B, cells with chromatid aberrations; $C_u$, cells with "unstable" chromosome aberrations, fragments, dicentrics, ring chromosomes; $C_s$, cells with "stable" chromosome aberrations, monocentric chromosomes due to translocations, etc. trisomies). In the presence of each fragment was considered as "one break," the presence of a dicentric chromosome was considered as "two

## Concentrations of the Solvents in the

The concentrations of benzene and homologues in April 1953, at the time of the epidemic of chronic benzene poisoning, were, in ppm of benzene, were: 131 ppm in the of the rotary machine room and solvent, 125 ppm near the windows of the counters, 363 ppm near a folding machine in the rotary machine room, and 532 ppm in the auxiliary room. All these concentrations above the maximal allowable concentration (MAC) (25 ppm of benzene), were taken in April at a time when windows were kept partly open; it is assumed that the concentrations may have been higher during the preceding winter months.[9]

The ink solvents examined proved to be benzene. Two types of ink diluents were used: one was technically pure benzene, and the other a mixture of benzene (55%), toluene (25%), and xylene (20%).[9]

After the epidemic of benzene poisoning, benzene was no longer used as an ink solvent or diluent; toluene with traces of xylene was substituted for benzene was substituted. The solvent in use at the time of this study was pure toluene.

Concentrations of toluene vapors in the ambient air in different parts of work areas ranged from 0 to 240 ppm in the years 1957 to 1967. Values for the years 1957 to 1967 are reported in Table 3. In 1966 the plant was renovated; the values shown for 1967, much lower than the previous ones, were obtained in the new printing department where ventilation has been greatly improved.

Mean concentrations were generally low and only sometimes just above the MAC for toluene (200 ppm) near the folding machines and in the center of the working room, but were well above the MAC between the printing elements. Since employees work mainly near the folding machines, and only occasionally for a few minutes between the machines, the time they are exposed to the MAC of toluene is most of their shifts, and to concentrations higher than the MAC for very short periods.

## Results

Chromosome studies in single su

Table 1.—*Wor*

| Age | Be |
|---|---|
| 38 | |
| 45 | |
| 45 | |
| 54 | |
| 54 | |
| 41 | |
| 47 | |
| 36 | |
| 45 | |
| *50* | |

* Numbers in parenth

Table 2.—*Exp*

| Age | Y Exc T |
|---|---|
| *29* | |
| 30 | |
| 32 | |
| 41 | |
| 32 | |
| 35 | |
| 32 | |
| 31 | |
| 35 | |
| 37 | |
| 42 | |
| 35 | |
| 39 | |
| 47 | |
| *30* | |
| 48 | |
| 38 | |
| 33 | |
| 34 | |
| *60* | |
| 45 | |
| 43 | |
| 55 | |
| 58 | |

Number in parenth

Table 1.—*Exposure* Data. Chromosome *Studies. and Hematological* Notes *of Ten Workers Exposed to Benzene Before 1953 and to Toluene After 1953*

| Age | Years of Exposure to Benzene | Years of Exposure to Toluene | Total Cells Studied | % Cells $C_u$ | % Cells $C_s$ | Hematological Notes |
|---|---|---|---|---|---|---|
| 38 | <1 | 14 | 100 | 1 | ... | Slight anemia in 1953 ana 1957 |
| 45 | 2 | ... | 100 | 2 | 2 | Severe benzene nemopathy in i353 |
| 45 | 3 | 14 | 64 | ... | * | Slight anemia in 1953, 1957, 1958. 1964 |
| 54 | 3 | 14 | 100 | ... | ... | Slignt anemia ana leukopenia in i953 |
| 54 | 3 | 14 | 100 | ... | ... | Slignt anemia in 1955 |
| 41 | 3 | ... | 100 | ... | 2 | Severe benzene ncmoparny in 1953 |
| 47 | >3 | 14 | 100 | 3 | 1 | Slight anemia in 1953 |
| 36 | 5 | 14 | 100 | 4(5)* | ... | Slignt anemia in 1954 |
| 45 | 7 | 14 | 100 | 2 | 1 | ... |
| 50 | 22 | 12 | 100 | 4(5)* | ... | ... |

* Numbers in parentheses indicate the calculated breaks in $C_u$ cells.

Table &—*Exposure* Dam, *Chromosome Studies. and Hematological Notes of 24 Workers Exposed Oniy to Toluene After 1953*

| Age | Years of Exposure to Toluene | Total Cells Studied | % Cells $C_u$ | % Cells $C_s$ | Hematological Notes |
|---|---|---|---|---|---|
| 29 | 3 | 100 | 1 | ... | Moderate thrombocytopenia in 1965 |
| 30 | 7 | 100 | ... | ... | ... |
| 32 | 7 | 100 | ... | ... | Slignt anemia in 1961, 1963. 1966. 1967 |
| 41 | 7 | 100 | ... | ... | ... |
| 32 | 7 | 100 | ... | ... | ... |
| 35 | 7 | 100 | ... | ... | ... |
| 32 | 7 | 100 | 1 | ... | ... |
| 31 | 7 | 100 | 2 | ... | ... |
| 35 | 8 | 100 | 3 | ... | ... |
| 37 | 10 | 100 | ... | ... | ... |
| 42 | 10 | 100 | ... | ... | ... |
| 35 | 10 | 100 | 1 | ... | ... |
| 39 | 10 | 100 | 1 | ... | ... |
| 47 | 10 | 100 | 2 | 1 | ... |
| 30 | 11 | 100 | ... | ... | ... |
| 48 | 11 | 100 | ... | ... | ... |
| 38 | 11 | 100 | ... | ... | ... |
| 33 | 11 | 100 | 1 | ... | Slight anemia in 1961. 1963 |
| 34 | 11 | 100 | 2(3)* | ... | Slignt anemia in 1957. 1960. 1962 |
| 60 | 12 | 100 | 3 | ... | ... |
| 45 | 13 | 100 | ... | ... | Slignt anemia in 1958 |
| 43 | 14 | 100 | 1 | ... | ... |
| 55 | If | 100 | ... | ... | Slignt anemia in 1955. 1966 |
| 58 | 15 | 100 | 1 | 1 | Slignt anemia since 1956 Mogerate leukopenia in 1960 |

* Number in parentheses indicates the calculated breaks in $C_u$ cells.

Table 3.—*Concentrations of Toluene Vapors in Different Parts of the Working Department*[a]

| Year | Toluene Concentrations (ppm) | | |
|---|---|---|---|
| | Center of Room | Near Folding Machines | Between Machine Elements |
| 1957 | 223 | 56 | 513 |
| 1958 | ... | 189 | 306 |
| 1959 | 234 | 200 | 322 |
| 1960 | 218 | 226 | 423 |
| 1961 | 140 | 186 | 431 |
| 1962 | 239 | 277 | 824 |
| 1963 | 150 | 213 | 338 |
| 1964 | 200 | 239 | 345 |
| 1965 | 213 | 239 | 372 |
| 1967 | ... | 156 | 265 |

[a] Mean values of many determinations.

Table 4.—*Chromosome Studies in the 34 Co... Matched With the Exposed Subjects*

| No. | Age | Matched With | Total Cells Studied | % C... $C_u$ |
|---|---|---|---|---|
| Controls of the subjects exposed to benzene &... | | | | |
| 1 | 38 | 1 | 100 | ... |
| 2 | 45 | 2 | 100 | ... |
| 3 | 47 | 3 | 100 | ... |
| 4 | 56 | 4 | 62 | ... |
| 5 | 58 | 5 | 65 | ... |
| 6 | 41 | 6 | 100 | 1 |
| 7 | 46 | 7 | 100 | ... |
| 8 | 37 | 8 | 100 | 2 |
| 9 | 42 | 9 | 100 | 1 |
| 10 | 49 | 10 | 100 | 2 |
| Controls of the subjects exposed only to toluene† | | | | |
| 11 | 25 | 1 | 100 | ... |
| 12 | 28 | 2 | 100 | ... |
| 13 | 32 | 3 | 100 | ... |
| 14 | 41 | 4 | 100 | 2 |
| 15 | 32 | 5 | 100 | ... |
| 16 | 35 | 6 | 100 | ... |
| 17 | 33 | 7 | 100 | 1 |
| 18 | 29 | 8 | 100 | 1(2)‡ |
| 19 | 35 | 9 | 100 | ... |
| 20 | 37 | 10 | 100 | 1 |
| 21 | 44 | 11 | 100 | 1 |
| 22 | 35 | 12 | 100 | 1 |
| 23 | 36 | 13 | 100 | 1(2)‡ |
| 24 | 46 | 14 | 100 | 1 |
| 25 | 29 | 15 | 100 | ... |
| 26 | 44 | 16 | 100 | 2 |
| 27 | 38 | 17 | 100 | ... |
| 28 | 32 | 18 | 100 | ... |
| 29 | 34 | 19 | 35 | ... |
| 30 | 60 | 20 | 100 | ... |
| 31 | 41 | 21 | 100 | 2 |
| 32 | 42 | 22 | 100 | 1 |
| 33 | 51 | 23 | 100 | ... |
| 34 | 55 | 24 | 100 | ... |

[a] Cases 1-10 in "Matched With" column same as those in Table 1.
† Cases 1-24 in "Matched With" column ... same as those in Table 2.
‡ Numbers *in* parentheses indicate the ca... breaks in $C_u$ cells.

in their matched controls are reported in Tables 1, 2, and 4. All data are *summarized* in Table 5. Data were analysed statistically by the $\chi^2$ test and, when possible, by the Wilcoxon matched-pairs test.

**Benzene Group Versus Controls**—The incidence of unstable chromosome changes ($C_u$) (1.66%) and of calculated breaks in $C_u$ cells (1.8%) were higher in the benzene group compared with controls (0.61 and 0.675, respectively); the difference was highly significant ($\chi^2 = 8.45$, $P < 0.01$ for $C_u$ cells; $\chi^2 = 9.96$, $P < 0.01$ for calculated breaks). The same was true for the frequency of stable chromosome changes ($\chi^2 = 7.51$, $P < 0.01$).

If one excludes from the benzene group the two subjects (*cases* 2 and 6) who had suffered from severe benzene hemopathy *in* 1953 (see Tabie 1), the frequency of $C_u$ cells was 1.83%; that of calculated breaks in $C_u$ cells, 2.09%; and that of $C_r$ cells, 0.26%. Such proportions are significantly higher than those for controls for $C_r$ cells and calculated breaks ($\chi^2 = 9.53$, $P < 0.01$ for $C_r$ cells: $\chi^2 = 11.87$, $P < 0.01$ for calculated breaks *in* $C_u$ cells). The rate of stable chromosome changes, though higher, did not differ significantly from that of the control group ($\chi^2 = 0.39$, $P > 0.05$).

**Toluene Gmup Versus Controls.**—In the toluene group the proportion of C, cells (0.8%) and of calculated breaks (0.83%) was somewhat higher than in the control group (0.61% and 0.67%, respectively), but the differences were not statistically signif-

Table 5.—*Freq... Expos...*

| Exposure Subjects | |
|---|---|
| Benzene (+ toluen... | |
| Toluene | |
| Control subjects | |

[a] Numbers in pare...

Table 5.—*Chro...*

| Exposure Subjects | |
|---|---|
| Benzene (+ toluen... | |
| Toluene | |
| Control subjects | |

...nt ($\chi^2 = 0.43$, $P > 0.$... 0.28, $P > 0.05$ for c... rate of $C_u$ cells was ... luene group (0.08%) a... 00)%), and the differe... nt ($\chi^2 = 0.11$, $P > 0.05$

**Benzene Group Versus ...**

...e frequencies of chrom... benzene group were h... ene group, and the di... ically significant ($\chi^2$ = ... cells: $^2\chi = 5.68$, $P < 0$... aks: $\chi^2 = 6.30$, $P < 0.0$

The data obtained in t... posed subjects and in t... ls (see Tables 1, 2, a... lysed by the Wilcox... The frequent occurre... same score greatly re... pairs useful for the anal... portions of unstable ar... e changes in the ben... nificantly higher than t... ls at the significance le... s: $t = 2$ for seven pair... four pairs).

...fferences in the propo... cells between the sub... ene and the controls we... cells: $t = 36.5$ for 1... 2 for three pairs).

Table 6 presents a summ... the chromosome coun... ups. The proportion of

some Studies in the 34 Con... ith the Exposed Subjects

| ...ched With | Total Cells Studied | ... $C_u$ |
|---|---|---|
| ects exposed to benzene & t... | | |
| 1 | 100 | ... |
| 2 | 100 | ... |
| 3 | 100 | ... |
| 4 | 62 | ... |
| 5 | 65 | ... |
| 6 | 100 | 1 |
| 7 | 100 | ... |
| 8 | 100 | 2 |
| 9 | 100 | 1 |
| 10 | 100 | 2 |
| ects exposed *onry* to toluene* | | |
| 1 | 100 | ... |
| 2 | 100 | ... |
| 3 | 100 | ... |
| 4 | 100 | 2 |
| S | 100 | ... |
| 6 | 100 | ... |
| 7 | 100 | 1 |
| 8 | 100 | 1(2); |
| 9 | 100 | ... |
| 10 | 100 | 1 |
| ** | 100 | A |
| 12 | 100 | 1 |
| 13 | 100 | 1(2); |
| 14 | 100 | 1 |
| 15 | 100 | ... |
| 16 | 100 | 2 |
| 17 | 100 | ... |
| 18 | 100 | ... |
| 19 | 35 | ... |
| 20 | 100 | ... |
| 2: | 100 | 2 |
| 22 | 100 | 1 |
| 23 | 100 | ... |
| 24 | 100 | ... |

1 "Matched With" column are ... Table 1.
1 "Matched With" column are ... Table 2.
Parentheses indicate the cal...

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**Table 5.—*Frequency of Unstable and Stable Chromosome Changes in Subjects Exposed to Benzene or Toluene or Both, and in 34 Controls***

| Exposure Subjects | No. of Cases | Age Range | Total Cells | % Cells $C_u$ | % Cells $C_s$ |
|---|---|---|---|---|---|
| Benzene (+ toluene) | 10 | 36-54 | 964 | 1.66(1.87)* | 0.62 |
| Toluene | 24 | 29-60 | 2.403 | 0.80(0.83)* | 0.08 |
| Control subjects | 34 | 25-60 | 3.262 | 0.61(0.67)* | 0.09 |

* Numbers in parentheses show percent of calculated breaks in $C_u$ cells.

**Table 6.—*Chromosome Counts in Subjects Exposed to Benzene or Toluene, or Both, and in 34 Controls***

| Exposure Subjects | No. of Cases | Total Cells Counted | % Cells With Chromosome Number <46 | 46 | >46(Polyploic) |
|---|---|---|---|---|---|
| Benzene (+ toluene) | 10 | 964 | 13.1 | 86.0 | 0.9(0.52) |
| Toluene | 24 | 2.400 | 14.3 | 85.4 | 0.3(0.29) |
| Control subjects | 34 | 3.262 | 10.2 | 89.5 | 0.3(0.3) |

: ($\chi^2 = 0.43$, $P > 0.05$ for $C_u$ cells; 0.23, $P > 0.05$ for calculated breaks). rate of $C_s$ cells was very similar in the ne group (0.08%) and in the controls "%), and the difference was not signif- : $\chi^2 = 0.11$, $P > 0.05$).

Benzene Group Versus Toluene Group.— frequencies of chromosome changes in benzene group were higher than in the ne group, and the differences were sta- ally significant ($\chi^2 = 4.22$, $P < 0.05$ for ells; $\chi^2 = 5.68$, $P < 0.05$ for calculated ks; $\chi^2 = 6.30$, $P < 0.05$ for $C_s$ cells). The data obtained in the two groups of ed subjects and in their matched cont- (* Tables 1, 2, and 4) were l i d by the Wilcoxon matched-pairs The frequent occurrence of pairs with same score greatly reduced the number airs useful for the analysis. However, the portions of unstable and stable chromo- e changes in the benzene group were ificantly higher than those in the con- at the significance level of 0.025 IC,, $t = 2$ for seven pairs; C, cells: $t = 0$ four pairs).

Differences in the proportions of C., and ells between the subjects exposed to ene and the controls were not significant ells: $t = 36.5$ for 13 pairs; $C_s$ cells: 2 for three pairs).

Table 6 presents a summary of the results the chromosome counts in the three ps. The proportion of aneuploid cells was similar in the three groups. A slightly higher rate of cells with more than 46 chromosomes was observed in the benzene group. This fact seemed mostly due to a higher rate of polyploid cells, but the difference was not statistically significant ($\chi^2 = 0.63$, $P > 0.05$).

## Comment

The increased proportion oi chromosome changes found in the subjects exposed to benzene in the past is in agreement with other reports.[4-7] Compared to the data oi Tough and Court Brown,[7] our series showed a lower incidence of stable chromosome changes, both in those exposed and in the controls. This may have been due to differences in methods used to assess stabie aberrations; in our study much of the work was done d e r direct observation, so that minor chromosomal changes, especially in chromosome groups B, C, and E might not have been detected.

The group of subjects exposed to toluene did show a somewhat higher rate oi unstable chromosome changes snd of calculated breaks compared to the controls. but the difference was not statistically significant. To our knowledge, no data on the chromosome status of workers exposed to toluene are available in the literature.

In the groups of subjects exposed to benzene, or toluene. or both the values were

somewhat dispersed (Tables 1 and 2). This was also true for the control group. In the benzene group no correlation existed between years of exposure or age and frequency of chromosome changes. It is known that the occurrence of bone marrow toxicity from benzene often does not correlate with intensity and length of exposure, but depends on individual factors. The group studied had a rather homogeneous degree of exposure, but severe benzene hemopathy had occurred in two subjects exposed for two and three years, respectively, and not in subjects exposed, respectively, for 5, 7, and 22 years (Table 1).

However, also among the controls the frequencies of chromosome changes were somewhat dispersed, suggesting a different individual susceptibility to chromosome damage in relation to unknown environmental factors.

From our data it is apparent that ... inhalation of toluene vapors at concentrations in the order of maximum ... values does not significantly increase the frequency of chromosome changes. Since the comparison was made with a group of subjects exposed to concentrations of benzene above the MAC, one cannot assume that toluene has absolutely no toxic effect on chromosomes or that effects are dose-...

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# The Effect ... Nitrogen Di... n Aldolase

... J. Ramazzotto, P... ...ore Jay Rappapor...

The effects of nitrogen c... ...me system of the rat ... studies were mad... ...pm) directly into the ...ge. The rates of flaw o... ...0, 3.0, 2.5, and 2.0 lite... ...d that there was incre... ...to exposures of the tiss... ...unt of $NO_2$ introduced ... was lowered, there wa... ...rence between expos... ...ps. Exposure at flows ... had an insignificant ...ity.

ALDOLASE is an int... ...h is found usually in ...cytoplasm.[1] In norma... ...s a small amount o... ...ted in the serum of ...thological condition... ...y is elevated.[2-4] When ...the fact that certain ...bly lead to patholog... ...sensibly suspect alte... ...ity due to air pollutar... ...is an air pollutant w... ...rette smoke and in urb... ...spheres and which h... ...ation for several ye... ...hum[5] considered the e... ...upon tissue following ...posure of live guinea p... ...nvestigations, there wa... ...ase activity due to ...e was also increased ...ity which could be due ...ng the release of the ti... ...blood.

...mitted for publication Ma... ...1.

...m the Department of Ph... ...try, Fairleigh Dickinson U...

...ant requests to Departm... ...l of Dentistry, Fairleigh Di... ...k, NJ 07666 (Dr. Ramazz...