Dichloromethane, methylene chloride (DCM)

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Citation for most recent IARC review

IARC Monographs 71, 1999

Current evaluation

Conclusion from the previous Monograph: Dichloromethane (DCM) is *possibly carcinogenic to human*s (Group 2B) based on sufficient evidence in experimental animals [lung and liver tumors in mice exposed by inhalation, and mammary tumors in rats (both sexes) exposed by inhalation].

Exposure and biomonitoring

Exposure

DCM is used primarily as a solvent in paint removers, degreasers, aerosol products and the manufacture of foam polymers. Production is estimated to be on the order of 2 X 10^8 kg/year in the United States (Watanabe et al., 2007 reporting from http:// www. atsdr.cdc. gov/tp14-c4.pdf). Exposure occurs during the manufacturing and use of consumer products. Occupation exposure occurs through its use as a degreaser, paint remover, aerosol propellant, blowing agent for polymer foam, and as a solvent in the textile industry, photographic film production (cellulose triacetate). The general public can be exposed from releases of DCM into the ambient air and water. Workers employed in furniture refinishing or furniture stripping are also exposed to DCM. The NIOSHTIC-2 database (NIOSH, 2009) contains multiple entries for reports involving methylene exposure and furniture stripping. Sources of exposures in indoor air come from spray painting paint removal and metal degreasing. DCM has also been found in some foods.

Biomononitoring

Exposure biomarkers

The available data on biomarkers of exposure for DCM are limited, and thus represent a major research gap. Three studies of DCM-exposed workers (ranging from 20 to 96 workers) have reported a positive correlation with urinary DCM (although small amounts) and time-weighted average DCM in the breathing-zone air of the workers (reviewed by Imbriani and Ghittori, 2005). No sex differences were observed. Ukai et al. (1998) stated that urinary DCM assays were sensitive enough to separate workers exposed to 10 ppm from non-exposed workers. Sakai et al. (2002) reported that urinary DCM levels increased with the start of exposure and decreased during lunch and dinner breaks in subjects with multiple samples.

The biological half life was estimated to be 210 to 410 minutes. Urinary levels of DCM did not differ according to *GST-T1* (a glutathione *S*-transferase of the theta class) genotypes, but a lower correlation (not statistically significant) was observed among workers with the cytochrome P450 (*CYP) 2E1 c1* allele than among the c2 allele. DCM is very volatile and thus sampling and storage conditions of biological fluids are important.

Biomarkers of effect

A dose-response relationship was observed between ambient levels of DCM (8-hour TWA) and carboxyhemoglobin concentrations among cellulose triacetate production workers who were non-smokers (Amsel et al., 2001). The formation of carboxyhemoglobin has been proposed to be a potential marker for estimating DCM exposure levels (Shusterman et al., 1990).

Human: Cancer in humans

(inadequate, Volume 71, 1999)

The previous IARC Monograph (71, 1999) reviewed seven cohort studies (photography film industry, textile fiber manufacturing industry and aircraft maintenance workers) and three case-control studies. The studies were limited by small numbers of exposed cases and few studies were able to evaluate exposure-response relationships. Excesses of several cancers were found in one or two cohort studies; pancreatic and breast cancer in two studies, and non-Hodgkin lymphoma, multiple myeloma, and cancer of the brain, cervix, prostate, liver and bile duct in one study. The case-control studies reported associations with astrocytic brain cancer, breast cancer, and rectal cancer; the risk of astrocytic brain cancer increased with increasing probability of exposure, duration of exposure and average intensity, but not cumulative exposure to DCM. The Working Group concluded that no type of cancer was elevated across studies to make a causal interpretation credible.

Since the 1999 IARC review, several more epidemiological studies have been published. These include an update (and/or expansion) of two of the cohort studies (Hearne and Pifer, 1999; Radican et al., 2009), one new cohort study (Goldberg and Thériault, 1994a, 1994b), an update of one of the case-control studies (Dumas et al., 2000), and four new case-control studies: CNS (Cocco et al., 1999), renal cell cancer (Dosemeci et al., 1999), childhood leukemia (Infante-Rivard et al., 2005), and lymphoma (Seidler et al., 2007). ~~The~~ Table 1 summarizes studies evaluating cancer and DCM exposure in tabular format. [This table is an updated version of the supplemental tables to the review by Ruder (2006)]. In addition, Ojajävi et al. (2001) conducted a meta-analysis of exposure to DCM and pancreatic cancer using four of the cohort studies that were part of the 1999 IARC review. The authors reported a meta-relative risk (MRR) of 1.42, 95% CI = 0.80 to 2.53.

Cohort studies

Hearne and Pifer (1999) reported the findings of two overlapping cohorts of photograph film-manufacturing workers at Eastman Kodak. [Cohort I was an update of the cohort described by Hearne et al., (1990)]. Statistically non-significant increased SMRs were reported for several cancers including stomach, brain and CNS, colorectal (only one cohort), pancreatic (only one cohort), leukemia, and Hodgkin lymphoma. Risks of leukemia ($P = 0.01$) (both cohorts) and pancreatic cancer ($P = 0.08$) (Cohort 1) increased with increasing cumulative

exposure to DCM. In an update of aircraft maintenance workers exposed to solvents, increased risks were observed for non-Hodgkin lymphoma and multiple myeloma among men, and breast cancer among women, confirming the findings from the earlier cohort (Radican et al., 2009). The third cohort study found statistically significant increased risks for (1) non-Hodgkin lymphoma among textile workers employed in the extrusion units (acetate, DCM or polypropylene depending on the time period) (Goldberg and Thériault, 1994a), and (2) colon cancer among male workers in the polypropylene and cellulose triacetate extrusion unit (Goldbert and Thériault, 1994b). Risks for both cancers increased with increasing exposure duration (This study did not measure exposure to DCM but the authors stated it was used during extrusion of cellulose triacetate.)

Case-control studies

Increased risks were found for CNS cancer (although risks did not increase with increasing probability or intensity of exposure) (Cocci et al., 1999), rectal cancer (with substantial exposure) (Dumas et al., 2000), and lymphoma (at the highest exposure level) (Seider et al., 2007), but not for renal cell cancer (Dosemeci et al., 1999). Increased risks (although not statistically significant) were also found for childhood leukemia and maternal exposure to DCM in a population based case-control study (Infante-Rivard et al., 2005).

In summary, excesses of cancer (lymphohemaopoietic, brain or CNS, pancreas, and breast) have been found in some studies but the findings for a specific site are not consistent across studies. The studies published since the IARC review provide some additional support for an association between exposure to DCM and lymphohematopoietic cancer. There is some site-concordance with animal studies for brain and breast cancer. The cohort study by Hearne and Pifer (1999) is probably the most informative study because it was able to evaluate exposure-response relationships. Most of the tumor sites of interests are rare or uncommon tumors, and the available cohort studies do not provide the power to detect these tumor. Few studies included adequate numbers of women, and thus there is very limited information for the evaluation of breast cancer. Some of the cohorts are young cohorts. None of the studies used biomarkers to measure exposure.

Animal: Cancer data in experimental animals

(*sufficient***,** Vol 77, 1999)

No chronic studies of DCM for carcinogenicity in rats or mice have been conducted since the 1999 IARC evaluation. In $B6C3F_1$ mice there is evidence of liver and lung tumors with inhalation exposures in both sexes, and liver tumors with drinking water exposures in males. In rats there is evidence of a trend for increased risk of liver tumors in female F344 rats exposed via drinking water or inhalation. Additional tumorigenic potential of DCM is provided by increased benign mammary tumors following inhalation exposure and the presence of the relatively rare astrocytoma or glioma tumors at relatively low exposure concentrations in rats. Although not as strong as mouse data, on the whole the rat data provide supporting evidence of carcinogenicity.

Mechanisms of carcinogenicity

Previously no genetic and related effects data were noted by IARC to be available in humans. DCM is positive for mutagenicity in a number of *Salmonella typhimurium* strains with and

without addition of exogenous metabolic activation. In mammalian systems, studies published before 1985 were primarily negative. In more recent publications, positive results have been reported for assays [DNA damage and HPRT mutations conducted in the mid 1990s by Graves et al., (1995, 1996)]. Since the IARC DCM evaluation, a few more *in vivo* studies have reported positive results (Rodriguez-Arnaiz, 1998; Sasaki et al., 1998). For *in vivo* genotoxicity, many more studies have been conducted in mice for lung and liver than in rat so it is difficult to link key events or results with positive cancer bioassays across rats and mice, which is a limitation of the database.

DCM is thought to be metabolized via two pathways, one involving *CYP2E1* and the other *GST-T1*. There is experimental evidence exists that indicates manipulation of the glutathione (GSH) pathway can alter toxicity (i.e., enhanced GST metabolism in bacteria results in greater genotoxicity. In humans, there is evidence of large individual variability in the rate of metabolism for both pathway; these include lifestyle factor induction of *CYP2E1,* and polymorphisms in *CYP2E1* and *GST-T1 (*e.g., the distribution *of GST-T1* polymorphisms varies among ethnic groups and were estimated to be 32% for wild (+/+), 48% +/- (heterozygote), and 20% -/- (null) among Caucasians) (Haber et al., 2001). Although concentrated in the liver, there is evidence of *CYP2E1* activity in the brain (Nishimura et al., 2003; Miksys and Tyndale, 2004). The variability in metabolism can be key for how epidemiological studies can examine and take into account DCM-induced toxicity or cancer.

Although the previous IARC evaluation placed emphasis on the GST pathway as the probable toxicity induction pathway, Landi et al. (2003) report that in primary cultures of human epithelial cells from 4 healthy human subjects there was DNA damage (comet assay) in 2 of the 4 cultures (2 subjects were *GST* + and 2 were *GST* -) after DCM exposure. However, there was no correlation with DNA damage and GST phenotype; GST activity was low in all cultures. Activity in half of this limited sample is suggestive of GST-independent genotoxicity. This finding, along with the positive genotoxicity assays without additional metabolic activation, raises issues regarding the proposed mode of action (MOA) of DCM. New literature on the metabolism of DCM also raises issues of which pathways, what actions of metabolites, and how manipulations of the GSH pathway are responsible for DCM carcinogenicity (Watanabe et al., 2007; Watanabe and Guengerich, 2006). Watanabe and Guengerich (2006) demonstrated that formyl chloride (a P450 metabolite of DCM) does not react with GSH. Watanabe et al. (2007) examined male and female rats and mice treated with DCM for GSH-linked DNA adducts using a relatively sensitive technique. Despite overcoming difficult technical problems, Watanabe and Guengerich (2007) reported no DCM GSH-adducts were detectable *in vivo*. More research needs to be conducted on these pathways and metabolites. Several PBPK models use assumptions about metabolism and the importance of these pathways in determination of the relevance of human risk. Uncertainties raised by the data gaps for pathway toxicity affect the accuracy of the models and inferences from them.

Research needs and recommendations

Human cancer studies

Identification of possible new cohorts for future epidemiologic studies should be undertaken. Such cohorts may include auto repair technicians (Enander et al., 2004) and furniture-

stripping workers (NIOSH, 2009). Larger or multi-plant cohort studies, that include women, need to be conducted with rigorous exposure assessment that allows for the evaluation of exposure response relationships. The studies should use internal or nested case control analyses to help reduce potential confounding. Case-control studies should be conducted for lymphohematopoietic cancer, and cancers of the breast and brain. The working group is aware of several large brain case-control studies (NCI, NIOSH, Interphone), which will be analyzed in the next year or two for an association between exposure to chlorinated solvents and risk of brain cancer (Inskip et al., 2001; Ruder et al., 2006; Cardis et al., 2007).

Ideally the studies should look at cancer incidence, especially when looking at lymphomas. If possible, medical records, or data on molecular markers of lymphoma should be obtained to provide more information on the diagnosis of lymphohematopoietic cancers (For further discussion, see the TCE review). The validation of urinary DCM as a useful biomarker of exposure needs to be done for its use in epidemiological studies.

A meta-analyses approach is also warranted given the modest relative risk estimates and the relative rarity of the cancers observed, and therefore the limited statistical power of individual studies.

Genetic susceptibility studies

Studies looking at genetic susceptibility are useful for understanding mechanisms and increasing the power to detect an effect. Candidate genes include *GST-T1* and *CYP2E1*. Large studies are needed to be able to detect gene-environment interactions. Other candidate genes for genetic susceptibility includes those involve in regulating immune function. Studies should also be conducted using entire genome scans to identify new susceptibility genes.

Genetic-related genomic damage studies

Studies evaluating genetic damage (such as adducts, mutations, chromosomal aberrations, micronuclei and sister chromatid exchange) are also needed. These studies should also include look at genetic susceptibility such as *GST-T1* and *CYP2E1*. These studies could be conducted among the Eastman Kodak workers in the cohorts established by Hearne and Pifer (1999) since this study had sampling data for DCM and was able to calculate cumulative exposure.

Mechanistic concerns

Research needed includes the (1) identification and role of metabolic pathways involved in carcinogenicity, (2) identification of modes of actions from the numerous toxicologically active metabolites of the solvents, and (3) development and validation of physiologically based pharmacokinetic (PBPK) modeling. Measurements of DCM levels need to be a part of future studies with further development of biomarkers.

Immunologic mechanism may be involved in lymphomagenesis from solvents (Vineis et al., 2007) and this should also be an area of future research. Brain tumor is also a potential target for DCM, and Perc (tetrachloroethylene), and has not been adequately studied for TCE.

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TABLE 1. Cancer Studies Evaluating Occupational Exposure To DMC (adapted from Ruder 2006)

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Bond et al. 1990	Dow Chemical	Case-control nested in cohort	44 cases, 1,888 controls	Liver & biliary tract ca death	All employed in chemical production 1940-82, VS to 1982, controls randomly selected from cohort of 21,437	Work histories to classify by exp potential to 11 substances (any/none)	Carbon tet, chloroform, PCE, 1,1,2-trichloro-ethane, vinyl chloride, PCB, dioxins, TCP, ethylene dibromide & dichloride	Exp: 4.6% cases, 8.9% controls RR 0.8 (0.2-3.6)	Workers could have had multiple exp, exp not quantified or qualified
Cantor et al. 1995	US NCI	Case-control (death certifi-cates)	33,509 cases, 117,794 controls	Breast cancer mortality in women	Died 1984-1989 in state where job and industry were coded, 4 controls with noncancer death/case	Job-exposure matrix: probability of exposure & level of exposure (0-4)	30 other substances	Whites: 5,416 deaths exp level 1 adj OR 0.95 (0.90-0.98), 1,298 deaths level 2 adj OR 1.04 (0.97-1.1), 1,713 deaths level 3 adj OR 1.17 (1.1-1.3). Blacks: 1,552 deaths level 1 adj OR 1.01 (0.9-1.1), 238 deaths level 2 adj OR 1.12 (0.9-1.3), 232 deaths level 3 adj OR 1.46 (1.2-1.7)	"Usual" job reporting could be biased. No data about known breast ca risk factors. Exp inferred from job & industry coding. Low number with high probability exp 5 cases 37 controls (same numbers as for C tet)
Cocco et al. 1999	US NCI	Case-control (death certifi-cates)	12,980 cases, 51, 920 controls	CNS cancer in women	Died 1984-1992 in state where job and industry were coded, 4 controls with noncancer nonneurological COD/case	JEM for probability (0-3) & intensity (0-3) of exp	Solvents, chlorinated aliphatic hydrocarbons, EMF, lead, benzene, PAH, nitrosamines, pesticides, public contact	Any/none: CNS cancer OR 1.2 (1.1-1.3), meningioma OR 1.2 (0.7-2.2)	"Usual" job reporting could be biased. Exp inferred from job & industry coding
Dosemeci et al. 1999	US NCI	Case-control	438 cases, 687 controls	RCC diagnosis	RCC dx July 1988-1990, population-based controls	Industry, job linked to JEM	Other chlorinated solvents	Any/none OR adj age, gender, smoking, hyper-tension, diuretics, BMI: all 0.87 (0.6-1.2), men 0.85 (0.6-1.2), women 0.95 (0.4-2.2)	Gives % exp but not number exp. Est 70 cases 124 controls exp. Multiple exp

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Heineman et al. 1994, Gomez et al. 1994, Cocco et al. 1994	US NCI	Case-control	300 male cases, 320 male controls	Brain tumor mortality	Died 1978-1981 hospital-confirmed astrocytic brain tumor or other causes (minus CVD, epilepsy, suicide, homicide, cirrhosis, some ca), NOK interviewed	JEM for probablity of exp, cum= duration weighted by probability. 38% estimated exp. to Me Cl	JEMs also for other chlorinated solvents	Low cum exp OR adj age, location 0.9 (0.5-1.5), med adj OR 1.9 (1.1-3.2), high adj OR 1.2 (0.6-2.5), test for trend not statistically significant Using detailed coding: Exp probability low OR adj age, era exp, location 1.2 (0.7-3.0), med adj OR 1.5 (0.3-9.0), high adj OR 6.1 (1.1-43.8), test for trend not reported *test for trend calculated as p< 0.001)*	Low participation rate, Interviewed <50% (300/ 741 cases, 320/ 741 controls) Adjusting for exp by decade & doing detailed coding reduced numbers—24 exp cases v 104 or 121—but apparently also reduced exp misclassification & refined risk estimates
Dumas et al. 2000 (update of Siemiatycki et al. 1991)	Québec Institute Research Occup Health Safety & Health Research Funds; Canada Health, Natl Health Res-earch & Development, NCI	Case-control	257 cancer patients, 533 population controls	Cancer diagnosis	Males age 35-70, dx 9/79-6/85, resident in Montreal metropolitan area on electoral list	Reanalysis (rectal cancer only) adjusts for other exposures	Many	Rectal cancer: any exp OR 1.2 (0.5-2.8) substantial exp OR 3.8 (1.1-12.9)	Multiple exp. Low number with any/substantial exp (7/5 rectal ca cases)
Seidler et al. 2007	German Federal Office for Radiation Protection	Case-control	710 lymphoma cases, 710 population-based controls	Lymphoma	Cases dx in 6 German regions age 18-80; controls matched on region, gender, and age ± 1 year	Complete occupational history assigned intensity & frequency of DCM by case-status blinded industrial physician	TCE, carbon tet, Perc, benzene, toluene, xylene, styrene	RR for cumulative exposure RR for ppm-yr: 0 - 1.0 (ref); > 0–≤26.3 – 0.4 (0.2-1.0); 26.3–≤175–0.8 (0.3-1.9); >175–2.2 (0.4-11.6); test for trend p=0.4	No exposure measurements. Mixed exposures?

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Blair et al. 1998, Stewart et al. 1991 , Radican et al. 2008	US NCI	Retro-spective cohort mortality & cancer incidence	14,457 workers, 1,222 ever exposed to methylene chloride	Death/cancer diagnosis	Civilian aircraft maintenance workers s employed >1 y between 1952-956 at Hill AFB, VS to 1990	JEM (ever/never methylene chloride)	Also exposed to TCE, other solvents, all but 3,739 workers exposed to 1-25 chemicals	1998 update Any v. none: NHL 6 male deaths RR 3.0 (0.9-10.0); multiple myeloma 5 male deaths RR 3.4 (0.9-13.2); breast cancer 4 deaths RR 3.0 (1.0-8.8) 2008 update Any v. none: NHL 8 male deaths RR 2.0 (0.8-5.4); multiple myeloma 7 male deaths RR 2.6 (0.9-7.7); breast cancer 6 deaths RR 2.6 (1.0-5.7)	Mixed exposures. Evaluation by job title, not person
Gibbs et al. 1996	Hoechst Celanese	Retro-spective cohort	2187 male, 1024 female	Cause of death	Worked >3 mons cellulose triacetate fibers, on payroll 1970 or later, VS through 1989	High (350-700 ppm), low (50-100 ppm	methanol, acetone, finishing oils, cellulose fibers	Overall no excess mortality Prostate ca: 13 deaths high exp SMR 1.8 (0.95-3.1), 9 deaths low exp SMR 1.4 (0.6-2.7). SMR 2.1 among those with 20 y latency. Cervical ca: 6 deaths among exp SMR 3.2 (1.2-7.3)	Exposure 0-50 ppm & 100-350 ppm? Pre-NDI followup complete? % with 20 yrs since 1st exposure?

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Hearne & Pifer 1999 (update and expansion of Hearne et al. 1990)	Eastman Kodak	Retro-spective cohort	1311 men starting 1946, 1013 men working 1964-70	Cause of death	Cohort 1 began work in cellulose triacetate mfg ≥1946, median F/U 34 ys to 1994. Cohort 2 worked ≥1 yr 1964-70 in roll coating, median F/U35 ys	Cohort 1 mean exp 39 ppm 8 hr TWA, cohort 2 mean exp 26 ppm	Acetone, methanol	Brain ca, Hodgkins, elevated both cohorts. Combined: 10 deaths SMR 2.2 (1.0-4.1), 4 deaths SMR 2.4 (0.6-6.5), respectively Cohort 1- also excess mortality for stomach SMR = 1.5 (0.5-3.0), and leukemia (SMR 2.0 (0.9-4.1); Cohort 2- also excess cancer mortality for pancreas, SMR = 1.6 (0.7-3.1), esophageal, SMR = 1.3 (0.4-2.9), stomach, SMR = 14 (0.4-3.6). and leukemia, SMR = 1.4 (0.5-3.0) dose/response with career exposure, test for trend, p= 0.01 for leukemia (both cohorts), and 0.08 for pancreas (cohort 1)	Combined SMRs not presented
Lanes et al. 1993	Hoechst Celanese	Retro-spective cohort	1271 workers	Cause of death	Cellulose fiber production prep/extrusion depts. ≥3 mo between 1954-76, VS through 1990	8 hr TWA range LOD-1700 ppm. Medians in 3 areas 140, 280, 475 ppm	Acetone, methanol	172 deaths SMR 0.9 (0.8-1.0), 4 biliary-liver ca SMR 3.0 (0.8-7.6). 43 IHD SMR 0.9 (0.7-1.2)	No healthy worker effect. Can't compare to unexp (latter excluded from cohort)

Reference	Study support/ affiliation	Study design	N	Outcome studied	Eligibility criteria	Exposure level	Other solvents, other exposures	Outcomes, ratio† (CI)	Study design issues
Goldberg & Thériault, 1994a, 1994b	Celanese Canada	Retro-spective cohort & nested case-control (colorectal cancer)	7,487 men, 2,724 women	Cause of death, colo-rectal cancer diagnosis	Synthetic textile production	Methylene chloride in 2/30 cellulose triactetate extrusion machines for 2/22 y & in closed-circuit cellulose acetate process. Est. low levels	Acetone, methanol	RR (v referents) all ca: cellulose triacetate unit 1.18 (0.4-2.0) all cancers, 4.28 (1.18-14.89) NHL; cellulose acetate fiber 1.32 (1.0-1.7) all cancers; all extrusion unit 3.85 (1.07-13.42) NHL Test for trend with employment duration, p < 0.001 for NHL for both cellulose acetate fiber and all extrusion units. OR colon ca: <5 y cellulose triacetate 7.43 (0.8-65), 5+ y 9.21 (1.3-64), <5 y cellulose acetate 0.59 (0.2-2.3), 5-9 y 2.16 (0.4-13), 10+ y 1.74 (0.4-7.9).	Multiple comparisons, no exp measurements
Ott et al. 1985	Dow Chemical	Retro-spective cohort	1,919 men total cohort 226 in chlorinat-ed methane group	Cause of death	Chemical manufacturing 1994-1969	Chlorinated methane employment category	Methyl chloride, chloroform, carbon tetrachloride,	20 deaths, 9 cancer deaths, Elevated mortality for digestive cancers 1.8 (0.7-4.0), and pancreatic cancer 3.3 (0.7-9.7)	Expected deaths obtain from company rates
Shannon et al. 1988	McMaster University Medical Center	Retro-spective cohort	203 females and	Cause of cancer (incidence)	Canadian lamp-manufacturing workers. Incidence cases: 1964 to 1982	Coiling and wire drawing	Trichloroethylene, strong acids (e.g., sulfuric, nitric acids) and metals (e.g., arsenic, chromium)	19 cancer cases, excess breast SIR = 2.0 (0.9-4.0), > 15 greater employment 3.2 (95% CI 1.1-7.5)	Initiated because of a cluster of 5 cancer cases in coiling wire drawing
Tomenson et al. 1997	ICI Chemicals & Polymers	Retro-spective cohort	1473 exp, 312 unexp	Cause of death	Cellulose triacetate production, men working 1946-88. VS to 1994	JEM to est cum exp for 70%	Not reported	47 deaths SMR 0.7 (0.5-0.99) in unexp, 287 deaths SMR 0.7 (0.7-0.8) in exp;, 15 IHD deaths SMR .7 (0.4-1.2) in unexp, 114 IHD deaths SMR 0.9 (0.8-1.1), increasing with increasing cum exp *Overall RR death exp/unexp 1, IHD RR 92/74=1.2*	30% no cum exp assignment