Adverse effects of Vinylchloride on fertility and reproduction

A literature study

Conducted at the request of the Directorate General of Labour by:
the TNO-CIVO Toxicology and Nutrition Institute;
in cooperation with:
the Coronel Laboratory of Occupational and Environmental Health,
Faculty of Medicine, University of Amsterdam

Directoraat-Generaal van de Arbeid

S 73-10

Adverse effects of Vinylchloride on fertility and reproduction

A literature study

Conducted at the request of the Directorate General of Labour by:
the TNO-CIVO Toxicology and Nutrition Institute;
in cooperation with:
the Coronel Laboratory of Occupational and Environmental Health,
Faculty of Medicine, University of Amsterdam

Authors:
Herman B. W. M. Koëter
Willem G. H. Blijleven
Henriëtte C. Dreef-van der Meulen (TNO-CIVO)

Anne Stijkel
Reinier L. Zielhuis (Coronel Laboratory)

Supervision on behalf of the initiator:
G. Idema

October 1989

ISBN 90 5307 014 1

CONTENTS Page

1. Introduction 4

2. Animal data 4

2.1 Risk of exposure of female animals with respect to gonads, endocrine system and fertility 4
2.2 Risk of exposure of female animals with respect to gestation and prenatal development 5
2.3 Risk of exposure of female animals with respect to the offspring 6
2.4 Risk of exposure of male animals with respect to gonads, endocrine system and fertility 6
2.5 Risk of exposure of male animals with respect to gestation of the partner 6
2.6 Risk of exposure of male animals with respect to the offspring 6
2.7 Risk of exposure of both male and female animals (mating partners) with respect to gestation 7
2.8 Risk of exposure of both male and female animals (mating partners) with respect to the offspring 7
2.9 Discussion and conclusion animal data 7

3. Human data 8

3.1 Risk of exposure of women with respect to the reproductive organs, the endocrine system and fertility 8
3.2 Risk of exposure of women with respect to the infant via lactation 8
3.3 Risk of exposure of women with respect to infant through lactation 8

CONTENTS (continued) Page

3.4 Risk of exposure of males with respect to the reproductive organs, endocrine system and fertility 8
3.5 Risk of exposure of male workers with respect to pregnancy and offspring of the partner 10
3.6 Risk of exposure to pregnancy and offspring; environmental studies 10
3.7 Discussion and conclusion on human data 13

4. Summary and evaluation 13

5. Literature 13

ADVERSE EFFECTS OF VINYLCHLORIDE ON FERTILITY AND REPRODUCTION

1. Introduction

Vinyl chloride (VCM) is used as a monomer in the plastics industry (e.g. in the production of polyvinyl chloride), as a refrigerant, in organic synthesis, in the production of methylchloroform and as a component of propellant mixtures. The structure formula of vinylchloride is CH_2= CHCl.

Since 1974 the MAC has been lowered from 200 ppm to 1 ppm (2 mg/m³) because of the discovery of carcinogenic properties of the vinyl chloride monomer. The carcinogenic and mutagenic effects probably are more pronounced than the effects on reproduction.
Most data discussed in this review are quoted from the critical reviews of Barlow and Sullivan (1982) and Zielhuis et al. (1984). Since then, only a few new studies have been published.

2. Animal data

In 1982 Barlow and Sullivan published a detailed review on the reproductive hazards of vinyl chloride. Additional and more recent literature data dealing with the reproductive hazards of the compound is not available. In the following paragraphs the literature data and conclusions of Barlow and Sullivan (1982) are summarized.

2.1 Risks of exposure of female animals with respect to gonads, endocrine system and fertility

No data available.

2.2 Risks of exposure of female animals with respect to gestation and prenatal development

Summary of the literature data of Barlow and Sullivan (1982).

Species	Exposure	Dose	Effects	NAEL	Ref.
mice N=27-37 per group	day 6-15 of pregnancy	0,129,1291 mg/m³,7h/day, inhalation	1291 mg/m³:maternal toxicity, 5/29 died, decreased nr. of implants, and mean fetal weight, increased resorption rate, increased nr. of unfused sternebrae, delayed ossification of the sternebrae and skull	<1291 mg/m³ 7 h/d	John et al. (1977)
rat N=17-33 per group	day 6-15 of pregnancy	0,1291,6456 mg/m³,7h/day, inhalation	6456 mg/m³:increased absolute and relative maternal liver weight, increased incidence of ureter dilatetia	1291 mg/m³ 7 h/d	John et al. (1977)
rat N=13-28 per group	day 1-9, or 8-14,or 14-21 of pregnancy	0,4000 mg/m³, 24h/day, inhalation	maternal tox.: red. weight gain in week 3, increased rel. liver weight in week 1 and 2; increased resorption rate in week 1	< 4000 mg/m³ 24 h/d	Ungvary et al. (1978)
rat N=40 per group	throughout gestation	0,6.15 mg/m³ 24 h/day, inhalation.	embryolethality, fetal weight reduced, haematoma, encephalocoele, hydrocephalus, additional ossification centres in sternum	<6.15 mg/m³ 24 h/d	Mirkova et al. (1978)
rabbits N=7-20 per group	day 6-18 of pregnancy	0,1291,6456 mg/m³,7h/day, inhalation	1291:increase in delayed ossification of the sternebrae	<1291 mg/m³ 7 h/d	John et al. (1977)

2.3 Risks of exposure of female animals with respect to the offspring

Summary of the literature data of Barlow and Sullivan (1982).

Species	Exposure	Dose	Effects	NAEL	Ref.
rat N=?	throughout gestation	6.15 mg/m³ 24h/day, inhalation	changed liver functions in the off-spring at 1-2 months of age	<6.15 mg/m³ 24 h/d	Mirkova et al. (1978)
rat N=?	day 9-21 of pregnancy	1550,15495 mg/m³, inhalation	1550,15495 mg/m³: low birth weights	<1550 mg/m³	Bingham et al. (1979)

2.4 Risks of exposure of male animals with respect to gonads, endocrine system and fertility

Summary of the literature data of Barlow and Sullivan (1982).

Species	Exposure	Dose	Effects	NAEL	Ref.
mice N=20 per group	5 days folowed by a dominant lethal test	0,7748,25826, 77479 mg/m³, 6h/day, inhalation	none	77479 mg/m³ 6 h/d	Anderson et al. (1977)
rat N=12 per group	5 days/week for 11 weeks	0,129,645, 2582 mg/m³, 6h/day, inhalation.	2582 mg/m³:affected mating performance; 645, 2582 mg/m³: reduced fertility index	129 mg/m³ 6 h/d	Short et al. (1977)
rat N=?	9-12 months (chronic study)	0,645,2582 mg/m³	no effects on testes or accessory organs	>2582 mg/m³ 6 h/d	Short et al. (1977)

2.5 Risks of exposure of male animals with respect to gestation of the partner

No data available.

2.6 Risks of exposure of male animals with respect to the offspring

No data available.

2.7 Risks of exposure of both male and female animals (mating partners) with respect to gestation

No data available.

2.8 Risks of exposure of both male and female animals (mating partners) with respect to the offspring

No data available.

2.9 Discussion and conclusion animal data

Most of the experiments were performed with rats and mice. Only one study with rabbits was available; most studies applied high exposure levels, far above the present very low occupational exposure limits.

Concerning the risk of exposure of female animals with respect to gestation and prenatal development it is concluded by Barlow and Sullivan (1982), that doses of 1291-6456 mg/m³ have shown absence of teratogenicity and fetotoxicity in the rat and absence of teratogenicity in rabbits. Absence of teratogenicity was also shown in the mouse at 129-1291 mg/m³. The highest doses were toxic to the dam in all three species. Embryolethality and teratogenicity was claimed by Mirkova et al. (1978) in a study with rats that received 6.15 mg/m³ throughout pregnancy. However, this study was poorly reported and in view of the large difference in dose level between this and other negative studies, these results await confirmation.

Concerning the risks of exposure of female animals with respect to the offspring Barlow and Sullivan (1982) concluded that the reports are inadequate for proper assessment.

Concerning the risks of exposure of male animals with respect to fertility Barlow and Sullivan (1982) concluded that dominant lethal effects have not been observed in mice and rats exposed to clearly carcinogenic or near lethal effects of vinylchloride by inhalation. However, in the rat, findings indicative of reduced fertility have been seen following sub-acute exposure to 645 mg/m³.

The available data are insufficient with respect to the assesment of a NAEL.

3. Human data

3.1 Risk of exposure of women with respect to the reproduction organs, the endocrine system and fertility

No data found.

3.2 Risk of exposure of women with respect to pregnancy and offspring

Lindbohm et al. (1985) did not observe an increased risk of spontaneous abortions among female workers processing polymerized plastics or heated plastics made of vinyl chloride or styrene. The authors stated that owing to the low statistical power of the study only strong effects could be ruled out. (The likelyhood of detecting a twofold risk was 38% for exposure to thermal degradation products).

3.3 Risk of exposure of women with respect to the infant via lactation

No data found.

3.4 Risk of exposure of males with respect to the reproductive organs, the endocrine system and fertility

Barlow & Sullivan (1982) reviewed the studies of Walker (1975-1976). Walker (1976) has recorded loss of libido as one of the presenting symptoms in men exposed to high levels (unspecified) of vinyl chloride monomer (VCM) on at least one occasion. She examined a total of 37 men aged 26-59 years (average age 40 years) who had been employed at a polyvinyl chloride (PVC) manufacturing plant for 9 months to 5½ years (average 2 years 8 months). Thirty had at some time been reactor operators; 4 were maintenance men, 2 worked as "baggers" and 1 was a warehouseman. Symptoms and signs in order of frequency included excessive fatigue, cold hands, ache in bones, dyspnoea, paraesthesia, cold feet, muscle pain, impaired grip and loss of libido in 13/37 cases. Walker (1975) elsewhere described the men as suffering from impotence, but no further details have been given. Clinically the men showed signs of Raynaud's phenomenon, severe in some cases, and circulatory changes may account for some of the symptoms such as dyspnoea, pains in the limbs, paraesthesia and fatigue. It is not known whether such changes might also account for the reported loss of libido or potency.

Sanotskii et al. (1980, USSR) studied the reproductive function in 14 men occupationally exposed to vinyl chloride. The exposure level was occasionally somewhat above 30 mg/m³; the age of the men exposed was 20-40 years. The control group (n=7) consisted of workers from a machine factory.
The authors analysed the ejaculates with respect to volume, number of spermatozoa per ml, motility and shape with the following results:

exposure to VCM	number	volume of ejaculate (ml)	number of spermatozoa (milion/ml)	motility %	% with normal shape
< 5 years	2	6.7±1.6	20.0±24.8*	53.0± 5.3	89.0±1.9
5-9 years	8	2.4±0.48	99.0±21.7	56.8± 7.8*	85.1±2.3
≥ 10 years	4	2.9±0.90	31.2±15.6**	39.6±11.8**	84.0±5.4
controls	7	3.3±0.18	89.7± 5.8	79.5± 2.1	80.4±0.7

* = P < 0,05

** = P < 0,01

This study suggests a weak effect on the sperm count and motility; however, because of the rather variable results, the small number of workers examined and the lack of a design with respect to confounders, the study is little informative.

Makarov (1984, USSR, only available as summary) studied sexual disorders in 198 male workers in the plastics industry, exposed to methylmethacrylate and vinyl chloride; comparison with 95 controls (not specified). He used questionaire surveys supplemented for 32 exposed and 10 controls with hormone assays. Both chemicals inhibited sexual activity. Vinyl chloride seemed to act primarily via the central nervous system. Sexual dysfunction was seen in conjunction with other occupational diseases due to exposure to the monomers. Because of lack of data on study design and potential confounding factors, the study is little informative.

3.5 Risk of exposure of male workers with respect to pregnancy and offspring of the partner

Selikoff (1976, USA, quoted from Barlow and Sullivan, 1982) observed higher stillbirth and miscarriage rates in wives of VCM workers from two plants in the state of Georgia than in the state of Georgia as a whole. However, the reliability of the assessment of the rates both in the cases and in the Georgia registrate data is not known.

3.6 Risks of exposure to pregnancy and offspring; environmental studies

Zielhuis et al. (1984) reviewed the following studies:
Edmonds et al. (USA, 1975) studied the incidence of congenital abnormalities of the central nervous system (mainly anencephaly and spina bifida) from 1970 to 1974 in three cities in which PVC plants were situated; the state of Ohio served as control. The data were obtained from hospitals which participated in the Birth Defects Monitoring Program (BDMP). The incidence of neonates with abnormalities was higher in the three towns than in the state as a whole. In Painesville one hospital had registered 15 cases; live births directly before and after each case served as controls. No case parents, but two control fathers had been working in the PVC factory at the time of birth; significantly fewer case mothers than control mothers worked within 10 miles of the factory. Therefore, evidence of a relationship exposure to VCM did not exist.
Edmonds carried out another study (1977) on the incidence of congenital abnormalities of the central nervous system (CNS) in 17 areas with PVC plants and with at least one BDMP hospital; controls were always drawn from the whole state. Again, no relationship between assumed ambient exposure to VCM and the incidence of congenital abnormalities of the CNS was observed. However, if the investigator had compared towns with PVC plants and towns without such plants the design would have been more sensitive.
Infante (USA, 1976) and Infante et al. (USA 1976a, 1976b) studied the incidence of congenital abnormalities in three cities with PVC plants (Painesville, Ashtabula, Avon Lake) and compared this with the incidence in the whole area, in the whole state (Ohio), and in ten cities of comparable size for the period 1970-1973. The data, as regrouped by Downs et al. (1977),

are presented in table 1. The study by Infante et al. focused on the relative risks (RR) in the three cities as compared with the entire state: for live-born and stillborn neonates the RR for congenital abnormalities of the central nervous system was 2.97 (observed 25, expected 8.42). However, Downs et al. (1977) compared the incidences in each of the three cities with those in surrounding cities without PVC plants; in this way possible differences in life style, ambient factors, and other confounders were minimized to a large extent. A significantly increased incidence was observed in Painesville (at a PVC plant) but also in two control cities (Geneva, North Ridgeville). Therefore, no conclusive evidence of an increased risk related to environmental exposure exists.

Table 1 - Incidence of congenital abnormalities in 13 cities in relationship to possible ambient exposure to VCM (Downs et al., 1977)

Area	Number of neonates with congenital abnormalities per 1000 live births	Total number of live births	P
Ohio State	10.14	719.287	
Ashtabula (PVC plant) and	17.4	1.900	< 0.90
two surrounding cities	16.1	1.429	
Painesville (PVC plant) and	18.1	1.381	< 0.001
five surrounding cities	5.7	7.762	
Avon Lake (PVC plant) and	20.3	738	< 0.10
three surrounding cities	12.1	12.330	

Hatch et al. (1981) presented statistical considerations with respect to studies of reproductive effects after exposure to vinyl chloride. They recommended sample sizes for future studies in order to prevent false negative or false positive results:

reproductive endpoint	prevalence in unexposed population	RR to be detected with 80% power*	number required in each studies
neural tube defects	0,001/live birth	6,0	1862 livebirths
spontaneous abortions	0,15/pregnancies	1,8	174 mothers
spontaneous abortions	0,12/pregnancies	1,8	240 mothers

* = power calculated for $\alpha = 0,05$, two-tailed test

Theriault et al. (Canada, 1983) assessed the association between birth defects and exposure to ambient vinyl chloride. They compared the rate of birth defects and stillbirth rates in Shawinigan, whith a vinyl chloride polymerisation plant since 1943, and the rates in other communities. They correlated the monthly and seasonal variations in the rate of birth defects with the concentration of VCM in ambient air. They also correlated the geographic variation of birth defect rates with the estimates of VCM in the air levels in several residential areas. They finally compared a group of parents who gave birth to a malformed infant with a control group with a normal neonate with respect to residential and occupational history, as well as exposure to other risk factors known to generate birth defects.

This well documented study yielded the following results: the incidence of birth defects for infants born to residents of Shawinigan in 1966-1979 were significantly higher than in three control communities. There was no excess of stillbirths in Shawinigan. The excess in the rate of birth defects occurred for all types of defects. According to the authors most teratogens may induce very specific effects. They observed a seasonal variation in birth defect rates. This observation favours an asociation between the VCM concentration in the air and birth defect rates in the community. However, the geographical distribution of birth defects in Shawinigan was not correlated with the estimates of the VCM concentration in ambient air. The author also mentioned that the probability of finding an excess of birth defects in the highly exposed districts twice as high as in the poorly exposed ones was 80%. The probability would have been 99% if the excess had been three times as high. The findings of this study cannot be considered as conclusive.

3.7 Discussion and conclusions on human data

Most studies reviewed are environmental studies; therefore, it is not possible to establish whether any effect should be attributed to exposure of the father, of the mother or of both.
Studies of occupationally exposed subjects are not relevant for the present work environment because of the decrease of the previous MAC to 3 ppm in 1986.
The sample size in some studies was too small and therefore, the power was not sufficient to minimize the prevalence of false positive or negative data.
Further, there were no data available with respect to the environmental exposure in the Netherlands.
Further investigation on the possibility of reproductive effects on exposure to vinyl chloride do not appear to be opportune because of the decrease in exposure in recent years both at the factory floor and via the outdoor air after the establishment of mutagenic and carcinogenic properties of the vinyl chloride monomer.

4. Summary and evaluation

Both animal and human data are inadequate for the evaluation of risks with respect to the endocrine system, the reproductive organs and fertility.
Limited studies in animals have shown that vinylchloride is not teratogenic or embryotoxic at otherwise non-toxic doses. There are insufficient data with respect to the assessment of a NAEL.
Because of the already lowered MAC to 1 ppm after the assessment of carcinogenicity, further studies of effects on reproduction are not considered as opportune.

5. Literature

Anderson, D., M.C.E. Hodge and I.F.H. Purchase (1977)
Dominant lethal studies with the halogenated olefins vinyl chloride and vinylidene dichloride in male CD-1 mice.
Environmental Health Perspectives 21:71-78

Barlow, S.M. and F.M. Sullivan (1982)
Reproductive hazards of industrial chemicals.
Academic Press Inc., pag. 566-582

Bingham, E., J. Warkany and M. Radike (1979)
Teratological effects of vinyl chloride and ethanol in rats.
Annual Report ofPrPogram 1978-1979, pp. 140-143, Center for the Study of the human Environment, Department of Environmental Health, Kettering Laboratory, University of Cincinnati, U.S.A.

Downs, Th.D., R.A. Stallones, R.F. Frankowski and D.R. Labarthe (1977)
Vinyl chloride, birth defects and fetal wastage; a critical review.
Prep. for the Society of Plastic industries by Research Stastitics
(quoted by Zielhuis et al., 1984)

Edmonds, L., H. falch and J.E. Nissim (1975)
Congenital malformations and vinyl chloride.
Lancet II, 1098 (quoted by Zielhuis et al., 1984)

Hatch, M., J. Kline and Z. Stein (1981)
Power considerations in studies of reproductive effects of vinyl chloride and some structural analogs.
Environmental Health Perspectives 41:195-201

Infante, P.F. (1976)
Oncogenic and mutagenic risks in communities with polyvinyl chloride production facilities.
Anm. N.Y. Acad. Sci. 276:49-57 (quoted by Zielhuis et al., 1984)

Infante, P.F., J.K. Wagoner and A.J. McMichael et al. (1976a)
Genetic risks of vinyl chloride.
Lancet I, 734-735 (quoted by Zielhuis et al., 1984)

Infante, P.F., J.K. Wagoner and R.J. Waxweiler (1976b)
Carcinogenic, mutagenic and teratogenic risks associated with vinylchloride.
Mutation Research 41:131-142 (quoted by Zielhuis et al., 1984)

John, J.A., F.A. Smith, B.K.J. Leong and B.A. Schwetz (1977)
The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats and rabbits.
Toxicology and Applied Pharmacology 39:497-513

Lindbohm, M.L. K. Hemminki and P. Kyyrrönen (1985)
Spontaneous abortions among women employed in the plastics industry.
Am. J. Ind. Med. 8:579-586

Makarov, I.A. (1984)
Sexual disorders in male workers occupationally exposed to methylmethacrylate and vinyl chloride.
Gig. Tr. Prof. Zabol, nr. 6:19-23 (only available as summary)

Mirkova, E., A. Mihailova and M. Noska (1978)
Embryotoxic and teratogenic action of vinyl chloride.
Khigiena Zdraveopazvana 23 (5):440-443

Sanotskii, I.V., R.M. Dautian and V.I. Glushckenko (1980)
Study of the reproductive function in men exposed to chemicals.
Gig. Tr. Prof. Zabol, nr. 5:28-32

Short, R.D., J.L. Minor, J.M. Winston and C.C. Lee (1977)
A dominant lethal study in male rats after repeated exposures to vinyl chloride or vinylidene chloride.
Journal of Toxicology 3:965-968

Thériault, G., H. Iturra and S. Gingras (1983)
Evaluation of the association between birth defects and exposure to ambient vinyl chloride.
Teratology 27:359-370

Ungvary, G., A. Hudák, E. Tatrai, M. Lorincz and G. Folly (1978)
Effects of vinyl chloride exposure alone and in combination with Trypan Blue-applied systematically during all thirds of pregnancy on the fetuses of CFY rats.
Toxicology 11:45-54

Walker, A.E. (1975)
A preliminary report of a vascular abnormality occurring in men engaged in the manufactrue of polyvinyl chloride.
Britisch Journal of Dermatology 93:22-23 (quoted by Barlow & Sullivan, 1982)

Walker, A.E. (1976)
Clinical aspects of vinyl chloride disease: skin.
Proceedings of the Royal Society of Medicine 69:286-289 (quoted by Barlow & Sullivan, 1982)

Zielhuis, R.L., A. Stijkel, M.M. Verberk and M. van de Poel-Bot (1984)
Health risks to female workers in occupational exposure to chemical agents.
Springer Verlag, 120 pp. (42-43)