Health Council of the Netherlands

# Polyvinyl chloride

Evaluation of the carcinogenicity and genotoxicity

2013/22

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**Gezondheidsraad**
Health Council of the Netherlands

Aan de minister van Sociale Zaken en Werkgelegenheid

Onderwerp : aanbieding advies *Polyvinyl chloride*
Uw kenmerk : DGV/BMO-U-932542
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Geachte minister,

Graag bied ik u hierbij het advies aan over de gevolgen van beroepsmatige blootstelling aan polyvinylchloride.

Dit advies maakt deel uit van een uitgebreide reeks waarin kankerverwekkende stoffen worden geclassificeerd volgens richtlijnen van de Europese Unie. Het gaat om stoffen waaraan mensen tijdens de beroepsmatige uitoefening kunnen worden blootgesteld.

Dit advies is opgesteld door een vaste subcommissie van de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS), de Subcommissie Classificatie van carcinogene stoffen. Het advies is getoetst door de Beraadsgroep Gezondheid en omgeving van de Gezondheidsraad.

Ik heb dit advies vandaag ter kennisname toegezonden aan de staatssecretaris van Infrastructuur en Milieu en aan de minister van Volksgezondheid, Welzijn en Sport.

Met vriendelijke groet,

prof. dr. W.A. van Gool,
voorzitter

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Evaluation of the carcinogenicity and genotoxicity

Subcommittee on the Classification of Carcinogenic Substances of the
Dutch Expert Committee on Occupational Safety,
a Committee of the Health Council of the Netherlands

to:

the Minister of Social Affairs and Employment

No. 2013/22, The Hague, October 18, 2013

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is "to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research..." (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Infrastructure & the Environment, Social Affairs & Employment, Economic Affairs, and Education, Culture & Science. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

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***INAHTA***

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# Contents

# Samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid evalueert en beoordeelt de Gezondheidsraad de kankerverwekkende eigenschappen van stoffen waaraan mensen tijdens de beroepsmatige uitoefening kunnen worden blootgesteld. De evaluatie en beoordeling worden verricht door de subcommissie Classificatie van Carcinogene Stoffen van de Commissie Gezondheid en Beroepsmatige Blootstelling aan Stoffen van de Raad, hierna kortweg aangeduid als de commissie. In het voorliggende advies neemt de commissie polyvinylchloride onder de loep. Polyvinylchloride wordt geproduceerd uit vinylchloride en wordt vooral gebruikt in de bouw- en constructie-industrie, in auto-onderdelen, in consumentenproducten, in verpakkingen en als isolatie van electriciteitsdraad. Polyvinylchloride wordt gemengd met additieven, zoals weekmakers, stabilisatoren, vullers, kleurstoffen, vlamvertragers en biociden.

De commissie concludeert dat de gegevens over polyvinylchloride niet voldoende zijn om de kankerverwekkende eigenschappen te evalueren (categorie 3).*

* Volgens het classificatiesysteem van de Gezondheidsraad (zie bijlage H).

# Executive summary

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluates and judges the carcinogenic properties of substances to which workers are occupationally exposed. The evaluation is performed by the subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council. In this report, the Committee evaluated polyvinyl chloride. Polyvinyl chloride is produced from vinyl chloride and is mainly used in the building and construction industries, in automotive parts, in consumer goods, in packaging and as electrical wire insulation. Polyvinyl chloride is compounded with additives, such as plasticisers, stabilisers, fillers, colorants, flame retardants and biocides.

The Committee concludes that the available data are insufficient to evaluate the carcinogenic properties of polyvinyl chloride (category 3).*

* According to the classification system of the Health Council (see Annex H).

Chapter 1

# Scope

## 1.1 Background

In the Netherlands a special policy is in force with respect to occupational use and exposure to carcinogenic substances. Regarding this policy, the Minister of Social Affairs and Employment has asked the Health Council of the Netherlands to evaluate the carcinogenic properties of substances, and to propose a classification (see Annex A). In addition to classifying substances, the Health Council also assesses the genotoxic properties of the substance in question. The assessment and the proposal for a classification are expressed in the form of standard sentences (see Annex H).

This report contains the evaluation of the carcinogenicity of polyvinyl chloride, further referred to as PVC.

## 1.2 Committee and procedure

The evaluation is performed by the Subcommittee on Classifying Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council, hereafter called the Committee. The members of the Committee are listed in Annex B. The submission letter to the Minister can be found in Annex C.

In 2013, the President of the Health Council released a draft of the report for public review. The individuals and organisations that commented on the draft are listed in Annex D. The Committee has taken these comments into account in deciding on the final version of the report.

## 1.3 Data

The evaluation and recommendation of the Committee is based on scientific data, which are publicly available. The starting points of the Committees' reports are, if possible, the monographs of the International Agency for Research on Cancer (IARC). This means that the original sources of the studies, which are mentioned in the IARC-monograph, are reviewed only by the Committee when these are considered most relevant in assessing the carcinogenicity and genotoxicity of the substance in question. In the case of PVC, an IARC-monograph of vinyl chloride and polymers is available, of which the summary and conclusion with regard to PVC are inserted in Annex E.

More recently published data were retrieved from the databases Medline and XToxline, and Chemical Abstracts. The last updated online search was in August 2013. The relevant new data were included in this report.

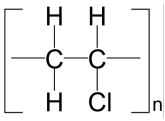
Chapter 2

# Polyvinyl chloride

## 2.1 Identity and general information

Polyvinyl chloride (PVC) is produced through the polymerisation of vinyl chloride. PVC resins for the production of rigid plastics are processed essentially without plasticiser: the polymer may be a homopolymer or a copolymer made with low levels of comonomer such as vinyl acetate or ethylene. The comonomers are used to aid in the processing of the resulting polymer. Most of the flexible and semi-rigid PVC plastics contain plasticisers at a level of 10-100% of the resin weight. The plasticisers most commonly used are dialkyl phthalates. Other compounding materials (such as pigments, fillers and light- and heat-stabilisers) are also used. PVC dispersion or paste resins are used in the form of plastisols (PVC resin dispersed in plasticiser).[1] PVC is mainly used in the building and construction industries, automotive parts, in consumer goods, packaging and electrical wire insulation.[1,2]

The identity of PVC and some of its physicochemical properties are given below.[1]

| | | |
|---|---|---|
| Chemical name | : | polyvinyl chloride |
| CAS registry number | : | 9002-86-2 |
| EC/EINECS number | : | not allocated |
| Synonyms | : | chloroethene homopolymer; atactic poly(vinyl chloride); chloroethylene polymer; poly(chloroethylene); poly(vinyl chloride); poly(vinylchloride); PVC; vinyl chloride homopolymer; vinyl chloride polymer |
| Colour and physical state | : | white or colourless granules |
| Molecular weight | : | 60,000-150,000 (average) |
| Molecular formula | : | $(C_2H_3Cl)_n$ |
| Structure | : |  |
| Relative density | : | 1.406 |
| Solubility | : | Solvents for unmodified PVC of high molecular weight are: cyclohexanone, methyl cyclohexanone, dimethyl formamide, nitrobenzene, tetrahydrofuran, isophorone and mesityl oxide. Solvents for lower polymers are: di-n-propyl ketone, methyl amyl ketone, methyl isobutyl ketone, acetonylacetone, methyl ethyl ketone, dioxane and methylene chloride. |
| Stability | : | PVC is unstable to heat and light in the absence of added stabilizers. Thermal decomposition products can include ethylene and aromatics such as benzene, toluene, 1,3,5-trichlorobenzene and naphthalene. |

## 2.2 IARC conclusion

In 1979, IARC concluded that the available studies on PVC are insufficient to evaluate the carcinogenicity of this compound.[1] Therefore, according to the IARC criteria, PVC was considered to be not classifiable as to its carcinogenicity to humans (Group 3).

Chapter 3

# Carcinogenicity studies

## 3.1 Observations in humans

Exposure of humans to PVC often cannot be separated from the exposure to vinyl chloride. IARC concluded that there is sufficient evidence in humans for the carcinogenicity of vinyl chloride, causing angiosarcoma of the liver and hepatocellular carcinoma, and subsequently classified vinyl chloride in Group 1 (carcinogenic to humans).[3] Most studies with PVC workers have focussed on exposure to vinyl chloride monomer, but might also provide information on the carcinogenicity of PVC. The Committee limits itself to studies specifically focusing on the exposure to PVC. These are summarised below, and presented in the Table in Annex F.

### Cohort studies

Gennaro et al.[4] reanalysed a VC-PVC production plant cohort previously studied by Mastrangelo et al.[5], by using an internal reference group. In total, 1,658 employees had worked in a large petrochemical plant for any period between July 1950 and July 1985; follow-up period extended from January 1972 to December 1999. Workers were classified according to their job categories (28 plant sectors) in four large, rather homogeneous groups: autoclave workers (who are associated with exposure to relatively high levels of vinyl chloride), PVC baggers, PVC compound workers, and other blue collar workers. Technicians

and clerks, considered as a group with low (or null) exposure was used as internal reference group. The analysis was performed using a Poisson regression model including age, calendar period of follow-up, age at hiring, year of hiring, duration of employment and latency.

A statistically increased risk mortality rate was found in autoclave workers for liver tumours, including angiosarcoma (relative risk (RR) 9.57; 95% CI 3.71-24.68). A non-significantly increased RR was found for lung cancer in PVC baggers (3.13; 0.96-10.28; $p < 0.10$) and liver tumours in PVC compound workers (2.46; 0.94-6.42; $p < 0.10$). The fourteen workers with lymphoid and haematopoietic cancer could not be compared to the referent group, because none were seen in the reference group. When compared to the Italian population statistically significant increased standardised mortality ratio (SMRs) were estimated for PVC baggers and for the total blue collar workforce, while PVC compound workers and other blue collar workers showed more than two-fold increase SMRs (not statistically significant).

The Committee notes that the elevated lung cancer relative risk in the baggers is difficult to interpret since it is based on a small internal comparison group with only three observed deaths from lung cancer. The comparisons with the internal reference group is the more doubtful given the all cause RR of 1.72 in the baggers and similarly high RR for all causes in the other sub cohorts.

Another retrospective cohort mortality study was executed in 5,498 male workers from nine chemical plants manufacturing or polymerising vinyl chloride in the UK.[6] Workers had to be employed for at least 1 year in a job that involved potential exposure to vinyl chloride for at least 25% of the workweek between 1940 and 1974, and were followed up to 31 December 1984. Workers were divided in 4 categories: autoclave operators, baggers and driers, craftsmen and other workers. The hygiene data available indicated that autoclave workers had the highest exposure to vinyl chloride, bagger and driers the highest PVC dust exposure (0.38-2.88 mg/m$^3$), and craftsmen intermediate exposure for both monomer and polymer. Mortality rates were compared to expected mortality rates of males in England and Wales matched for age.

A strong healthy worker effect was observed. A significant excess of nonsecondary liver cancer (mainly angiosarcomas) was reported in autoclave workers with a median latency period of 25 years from date of first exposure. Bagger and driers, and craftsmen showed a deficit of death caused by lung cancer (SMR 0.58 and 0.42, respectively; smoking was not considered as confounding factor).

Waxweiler et al.[7] performed a retrospective cohort study of 4,806 white male workers ever employed at a synthetic chemicals plant in Kentucky, US, from its opening in 1942 until 31 December 1973. Many of the workers had concomitant exposure to vinyl chloride monomer, as well as to chlorinated solvents, PVC dust, acrylates and acrylonitrile. In this cohort, a statistically significant risk of death due to malignant tumours of the central nervous system (SMR = 2.09; $p < 0.05$) and respiratory system (SMR = 1.49; $p < 0.01$) was observed compared to the US white male population. Also, an analysis including 10 years latency showed a slightly increased risk of death for respiratory system cancer (SMR 1.56).

To determine whether an excess risk existed for a particular histological type of lung cancer, Waxweiler et al. conducted a study design which was referred to as a case-comparand study. In this study the worker case group, consisting of the 27 of the 45 deceased individuals for whom histologic specimens were available, was compared with a lung cancer comparison group*. An excess of respiratory system cancer was found to be limited to adenocarcinoma (SMR 1.38; p not given) and especially, large cell undifferentiated lung cancer (SMR 4.41; p not given) when compared with the comparison group.

To evaluate the association between lung cancer and each of 19 chemicals at the plant, detailed work histories for each cohort member were combined with exposure ratings for each of 19 chemicals for each job for each calendar year since 1942. A serially additive expected dose model was then constructed which compared the doses of each chemical observed for the lung cancer cases to the doses expected based on subcohorts without lung cancer individually matched to the cases. PVC dust appeared to be the most likely etiologic agent ($p = 0.037$). Time trends of PVC dust exposure indicated a potential latent period of 5-16 years before death.

Wu et al. updated the cohort studied by Waxweiler et al. and extended the observation period from 1974 to 1986.[8] In the total cohort, a statistically significant increase in cancer risk was observed for liver, lung, and brain. In a subpopulation exposed to vinyl chloride (but potentially also to PVC), only an excess risk was observed for liver cancer.

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* Lung cancer cases most closely preceding and succeeding the chemical plant workers case in the chronologically ordered hospital pathology logs, matched in age at diagnosis, sex, race, and county of residence. Smoking was not investigated.

Ward combined and updated several cohort studies on vinyl chloride workers in Europe, accumulating in a cohort of 12,700 male workers.[9] The emphasis of this study was on exposure to VCM. No strong relation was observed between cumulative vinyl chloride exposure and cancers other than in liver.

Several additional analyses were done on the subcohort of packers and baggers, that was particularly exposed to PVC dust. The Committee notes that the reported results in this respect are somewhat ambiguous. Ward et al. report to have observed no trend in lung cancer risk with increasing exposure for persons ever worked as packer or bagger. However, these authors reported a positive trend in lung cancer in the persons who had only worked in these jobs. The exact findings with respect to lung cancer and PVC dust are not shown in the publication.

### Case-control studies

Mastrangelo et al.[5] conducted a nested case-control study among 543 claimants (out of a total cohort of 1658 workers) employed at an Italian vinyl chloride/PVC production plant. Thirty-eight cases of histologically confirmed lung cancer and 224 control subjects without a history of cancer were selected from the claimants. Four categories of exposure to PVC dust were determined: (0) subjects with the least exposure to PVC dust; (1) compounding workers, never baggers; (2) PVC baggers with several jobs at once, date of specific job change not indicated; (3) PVC baggers with known length of job, for whom start and end dates were available.

An odds ratio (OR) of 5.6 (95% CI 2.03-16.3) was found for PVC baggers with known duration of work. The lung cancer risk increased with the years working as a bagger ($\geq$ 3.6 years, OR 7.15; CI 2.55-19.3) and increasing age at onset of the job (over 33 years at onset, OR 7.70; CI 2.72-21.1). Both groups of baggers with calendar year at onset of job before 1967 or from 1967 onwards showed a significant increase of lung cancer compared to workers who had never been baggers (before 1967 OR 4.79; CI 1.73-12.5; $\geq$ 1967 OR 4.55; CI 1.38-13.6). Recent rather than historical exposure as a bagger results in a stronger association with lung cancer (> 20 years: OR 3.76; CI 1.51-8.99; $\leq$ 20 years: 11.4; CI 2.21-60.7).

No significant association with lung cancer was found for PVC compounding, cumulative vinyl chloride exposure, or age at the end of the period of observation. Correcting for smoking and age, an excess of lung cancer risk (OR 1.20; CI 1.08-1.35) was found for each extra year of work as a bagger compared

to workers never exposed to PVC, compounding workers, and baggers with unknown length of job.

Wu et al. updated the cohort described by Waxweiler et al. and case-control analyses to 31 December 1986, comprising 4,835 white males.[8] Exposure to PVC dust occurred primarily during the packing of the dried polymer, which was in the form of a powder. PVC dust exposure occurred in many of the same areas in which exposure to vinyl chloride occurred. Some workers were also exposed to butadiene.

Exposures for each chemical were rated from 0 (no exposure), 1 (exposure (chemical in building, not handled), 2 (moderate exposure; works around chemical), 3 (occasional high exposure; spill), 4 (high exposure) and 5 (intimate contact; e.g. cleaners). Case subjects were matched to 5 control subjects by age. The excess as reported by Waxweiler (1981) was not confirmed. No association was found for exposure to PVC dust and lung cancer, since average cumulative exposure to PVC dust was lower in the lung cancer cases than in the controls.

Hardell et al. reported a case-control study investigating a possible association between testicular cancer and exposure to PVC among the Swedish population.[10,11] Cases (n = 148) with testicular cancer and 30-75 years old were extracted from the Swedish Cancer Registry between 1989 and 1992. Controls (n = 315) were selected from the Swedish Population Registry as the next subject in birth registration order (born the same year) as the cases. Exposures to PVC plastics were confirmed by contact with the employers or the production managers.

Seven cases and two controls had been exposed to PVC resulting in an OR of 6.6 (95% CI 1.4-32) for testicular cancer. The latency period varied between 11 and 35 years. For cumulative exposure to PVC in the lowest exposure group with 3 cases and 2 controls an OR could be calculated of 2.6 (95% CI 0.3-3.2; latency period not specified).

Hardell et al. conducted a second case-control study for germ cell testicular cancer.[12] Each case (age 20-75 years and recorded in the period 1993-1997) was matched with one control, resulting in 791 matched pairs. Exposure was assessed with a questionnaire similar to the previous study, however with more detailed exposure on plastics exposure. Every work task was classified according to type of PVC contact with regard to dust levels. The one subject that had been exposed to vinyl chloride, i.e. had been working with production of PVC plastics, was excluded from analysis.

Overall exposure to PVC plastics gave an OR of 1.35 (CI 1.06-1.71) slightly increasing with a > 10 years latency period to 1.45 (CI 1.06-1.98). However, no increasing response was found at increasing concentration. Rather, an inverse relationship with the highest OR in the lowest exposure category was observed (independent of latency period). This inverse relationship between exposure and response was also apparent using an updated exposure estimation by Westberg et al.[13]

Selenskas et al. conducted a case-control study for deaths from pancreatic cancer from a cohort who had worked 7 months or more at a New Jersey plant between 1946 and 1967.[14] A total of 28 cases were included, and 5 controls per case.

For the work area vinyl and polyethylene processing with possible exposure to PVC for vinyl processing (9 cases; 40 controls) an excess risk was found for duration of employment > 16 years (RR 7.15; 95% CI 1.28-40.1). No trend with increasing duration was apparent. For resin pulverising, and resins and varnish no increased risk was found; for these work areas PVC was not considered as one of the major chemicals to which exposure was possible.

### Other

Chiazze et al.[15,16] reported a cross-sectional mortality study with 3,847 deaths of white employees of seventeen PVC fabricators during 1964-1973. Several exposure categories (no exposure, improbable, possible, definite or unknown exposure) separately and combined were compared to not exposed employees. Sex-race-cause-specific proportionate mortality ratios (PMRs) were calculated by comparing with the US mortality for the individual years 1964-1973. The ratios were significantly different from unity for all cancers combined, and for cancers of the digestive system and for other, unspecified cancers among both white males and white females. In females also PMRs for urinary cancer and breast cancer were statistically significantly increased.

The incidence of deaths due to breast cancer was further investigated by case-control analysis. A total of 44 breast cancer deaths and 134 controls matched for age and distributed among eight companies were available. Most of the cases and controls belonged to the no exposure or improbable exposure category (33/44 cases and 114/134 controls), leaving only small numbers that have been exposed (2 cases and 6 controls for the definite category). None of the relative risks was statistically significantly increased.

IARC reported a proportional mortality study, using death certificates from 1970-1972 of 707 male plastic workers (extruding, moulding, cutting, turning or otherwise machining plastics, and including PVC fabricating) resulted in a statistically significant excess of stomach cancer mortality (24 observed/16.4 expected; $p < 0.05$).[1]

IARC noted several limitations of the study (i.e. the use of proportionate mortality methodology, and the fact that not all deaths studied were among workers engaged in PVC activity).

### Summary

Several epidemiological studies are available, with different designs (i.e. retrospective cohort, case-control, cross-sectional mortality). Most of these studies do not specifically address – and do not quantify – exposure to PVC. The results are inconsistent, as some studies report an association between PVC and lung cancer or testicular cancer, while other studies do not.

## 3.2 Carcinogenicity studies in animals

### Inhalation

Groth et al. exposed rats, guinea pigs and monkeys by inhalation (6 hour/day, 5 days/week) for up to 22 months to a concentration of 13 mg PVC dust/$m^3$. The treatment and control groups each contained 80 rats, 40 guinea pigs and 10 monkeys. Autopsies on rats and guinea pigs were performed after 12 months of exposure and on monkeys after 22 months of exposure.[17]

Aggregates of alveolar macrophages containing PVC particles were found in the lungs of all animals. No gross abnormalities were seen in the lungs or other organs that could be related to the exposures.

A group of 48 rats (24 per sex) was exposed to PVC dust, at a concentration of 12 mg/$m^3$ for 7 hour/day, 5 days/week for 5 months.[18] Cumulative exposure amounted to 8,552 mg/$m^3$*hour. Forty-eight control animals were not exposed. For each group, 6 rats were sacrificed at the end of the exposure period, 6 additional animals were sacrificed a year after the start of the exposure and the remaining animals were allowed to die of natural causes.

Widespread distribution of PVC particles was observed in all animals. There was evidence of a slight proliferation of reticulin fibers around some foci of

macrophages in the spleen, however no progression was observed in any of the animals.

### Oral

No oral studies are available.

### Dermal

No dermal studies are available.

### Other routes

A number of carcinogenicity studies with subcutaneously transplanted PVC have been reported in 1979 by IARC and hereafter, describing the induction of malignant fibrous histiocytomas by the implant.[1,19,24,25] No clearly increased incidence of tumours was found after intraperitoneal or intrapleural injection of granulair PVC.[18,20]

As these exposure routes are not relevant for occupational situation, these studies are only presented in Annex G.

## 3.3 Conclusion

The Committee notes that the available epidemiological data are inconsistent. As the exposure of PVC has not been properly assessed, co-exposures or general dust toxicity could have attributed to the inconsistent findings. The Committee concludes that the human data are insufficient to draw any conclusions on the carcinogenic properties of PVC in humans.

The Committee considers the available animal data not sufficient to draw conclusions on the carcinogenicity of PVC in animals.

Chapter 4

# Genotoxicity

## 4.1 Gene mutations assays

### *4.1.1 In vitro assays*

PVC did not induce reverse mutations in *S. typhimurium* TA97, TA98, TA100 and TA1535 with and without metabolic activation.[21]

In vivo assays

No data are available.

## 4.2 Chromosomal aberrations

### *4.2.1 In vitro assays*

No data are available.

### *4.2.2 In vivo assays*

Suskov and Sazonova (1982) reported a cytogenetic analysis in peripheral lymphocytes of 52 workers exposed to synthetic resins, including PVC resin.[22] The average reported concentration of PVC in the air of working areas was

6 mg/m$^3$. Seventy-four healthy individuals with no occupational contacts with synthetic resins and matched for sex, smoking, alcohol consumption and medication served as controls. A statistically significant increase in the average frequency of cells with chromosome aberrations of 6.1% was found for PVC compared to 2.4% for the controls. The spectrum of chromosome aberrations, i.e. mainly single and paired fragments, was also significantly different from the control. The Committee notes the potential of co-exposure and the limitations in reporting of the study.

## 4.3 Conclusion

The Committee concludes that there are insufficient data available to draw conclusions on the genotoxicity of PVC.

Chapter 5

# Classification

## 5.1 Evaluation of data on carcinogenicity and genotoxicity

The epidemiological studies available showed no consistent evidence for carcinogenicity of PVC in humans. Some studies show an association between certain cancer types and workers involved in PVC handling, whereas others do not. As these studies show serious methodological limitations (e.g. lacking a reliable exposure assessment of PVC, limited correction for confounders including co-exposures), the Committee considers the human data insufficient to draw any conclusions on the carcinogenic properties of PVC in humans.

A chronic inhalation study is available in rats, ginea pigs and monkeys, in which no (pre-)malignant lesions were observed. This study, however, was not aimed to identify carcinogenic effects and shows several methodological limitations, such as the use of only one dose level, lack of a sufficient follow-up period, and proper histopathologic analysis and reporting. Other carcinogenicity studies did not address a relevant route of exposure. Due to the lack of reliable carcinogenicity data, the Committee cannot draw conclusions on the carcinogenicity of PVC in animals.

PVC did not induce reverse mutations in *S. typhimurium* with or without metabolic activation. A study in PVC fabrication workers showed an increased number of chromosomal aberrations, however this study showed severe limitations in reporting and design. The Committee notes that there is insufficient information on the potential genotoxic mode of action of PVC.

## 5.2 Recommendation for classification

The Committee concludes that the data on PVC are insufficient to evaluate the carcinogenic properties (category 3).*

* According to the classification system of the Health Council (see Annex H).

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|---|---|
| A | Request for advice |
| B | The Committee |
| C | Submission letter |
| D | Comments on the public review draft |
| E | IARC Monograph |
| F | Human studies |
| G | Animal studies |
| H | Carcinogenic classification of substances by the Committee |

# Annexes

Annex **A**

# Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advice the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request

for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10-4 and 10-6 per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the committee is given in Annex B.

Annex **B**

# The Committee

- R.A. Woutersen, *chairman*
  Toxicologic Pathologist, TNO Innovation for Life, Zeist; Professor of Translational Toxicology, Wageningen University and Research Centre, Wageningen
- J. van Benthem
  Genetic Toxicologist, National Institute for Public Health and the Environment, Bilthoven
- P.J. Boogaard
  Toxicologist, SHELL International BV, The Hague
- G.J. Mulder
  Emeritus Professor of Toxicology, Leiden University, Leiden
- Ms M.J.M. Nivard
  Molecular Biologist and Genetic Toxicologist, Leiden University Medical Center, Leiden
- G.M.H. Swaen
  Epidemiologist, Dow Chemical NV, Terneuzen *(until April 1, 2013);*
  Exponent, Menlo Park, United States *(from August 15, 2013)*
- E.J.J. van Zoelen
  Professor of Cell Biology, Radboud University Nijmegen, Nijmegen
- S.R. Vink, *scientific secretary*
  Health Council of the Netherlands, The Hague

## The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the chairperson and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the inaugural meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

# Submission letter

Subject : Submission of the advisory report *Polyvinyl chloride*
Your Reference : DGV/MBO/U-932542
Our reference : U-7911/SV/fs/246-Z18
Enclosed : 1
Date : October 18, 2013

Dear Minister,

I hereby submit the advisory report on the effects of occupational exposure to polyvinyl chloride.

This advisory report is part of an extensive series in which carcinogenic substances are classified in accordance with European Union guidelines. This involves substances to which people can be exposed while pursuing their occupation.

The advisory report was prepared by the Subcommittee on the Classification of Carcinogenic Substances, a permanent subcommittee of the Health Council's Dutch Expert Committee on Occupational Safety. The advisory report has been

assessed by the Health Council's Standing Committee on Health and the Environment.

I have today sent copies of this advisory report to the State Secretary of Infrastructure and the Environment and to the Minister of Health, Welfare and Sport, for their consideration.

Yours sincerely,

(signed)
Professor W.A. van Gool,
President

Annex **D**

# Comments on the public review draft

A draft of the present report was released in 2013 for public review. The following organisations and persons have commented on the draft document:

- Mr. T.J.Lentz, National Institute for Occupational Safety and Health, USA.

Annex **E**

# IARC Monograph

**Excerpt from VOL: 19 (1979)**

Vinyl chloride, polyvinyl chloride and vinyl chloride acetate copolymenrs

CAS No.: 9002-86-2

Summary of Data Reported and Evaluation

## Experimental data

Polyvinyl chloride was tested in rats by subcutaneous and intraperitoneal implantation; local sarcomas were induced, the incidence of which varied with the size and form of the implant.

## Human data

In two proportionate mortality studies, in which death certificates of workers who had been involved in the fabrication of plastics, including polyvinyl chloride, were analysed, there appeared to be an increased proportion of cancer of the digestive system in both sexes and possibly of the urinary system and of the breast in women.

## Evaluation

The available studies on polyvinyl chloride, which indicate an elevated proportion of digestive system cancer in male and female workers and possibly of cancers of the breast and urinary organs in female workers involved in the fabrication of plastics, including polyvinyl chloride, are insufficient to evaluate the carcinogenicity of this compound.

Annex **F**

# Human studies

| Study type | Population | Exposure | Exposure duration / Follow-up | Effect | Relative Ratio (95% CI) |
|---|---|---|---|---|---|
| Cohort Gennaro et al. (2008) | workers from large petrochemical plant located in Porto Marghera (Venezia, Italia) for any period between July 1950 and July 1985 (n = 1,658) | Classified according to job categories (28 plant sectors) in four large, rather homogeneous groups: autoclave workers (n = 210), PVC baggers (n = 198), PVC compound workers (n = 404) and technicians and clerks (n = 202); one more heterogeneous group was categorized "other blue collar workers" (remaining 24 plant sectors; n = 644); internal reference = technicians and clerks | total person-years 42,253 / Jan 1972 - Dec 1999 | liver cancer<br>• autoclave workers<br>• PVC compound workers<br><br>lung cancer (PVC baggers)<br><br>lymphatic and haematopoietic cancer (compared to Italian population)<br>• PVC baggers<br>• total blue collar workforce<br>• PVC compound workers<br>• other blue collar workers | RR<br>9.57 (3.71-24.68) p<0.05<br>2.46 (0.94-6.42) p<0.10<br><br>3.13 (0.96-10.28) p<0.10<br><br><br>SMR<br>3.77 (1.03-9.66)<br>2.27 (1.24-2.81)<br>2.26 (not stat. sign.)<br>2.29 (not stat. sign.) |

| | | | | | |
|---|---|---|---|---|---|
| retrospective cohort (control: population of England and Wales) Jones et al. (1988) | male workers from 9 plants manufacturing or polymerizing vinyl chloride and exposed ≥1 year between 1940-1974 (n = 5,498) | 0.23-0.46 (autoclave operators)<br>0.38-2.88 (baggers and driers)<br>0.52-0.84 (craftsmen)<br>≤0.93 mg/m$^3$ (other workers) | ≥1 y /<br>10-44 y | liver angiosarcoma<br><br>lung cancer | SMR<br>autoclave: 18.42 (7.41-37.95)<br>autoclave: 0.58 (CI not reported)<br>craftsmen: 0.42 (CI not reported) |
| retrospective cohort (control: US white male population) Waxweiler et al. (1981) | white male workers ever employed at synthetic chemicals plant in Kentucky, US from opening in 1942-1973 (n = 4,806) | no data | no data /<br>until 31 Dec 1973 | cancer of central nervous system<br>cancer of respiratory system<br>cancer of respiratory system (10 y latency) | SMR<br>2.09; p<0.05<br>1.49; p<0.01<br>1.56; significant, p not given |
| retrospective cohort (control: white men in US) Wu et al. (1989) | male workers from a PVC polymerization plant in the US employed between 1942 and 1974 (n = 4,835) | PVC dust was not quantified. Also exposure possible to butadiene due to production of styrene-butadiene rubber | ≤32 y /<br>until 31 dec 1986 | whole cohort:<br>liver cancer 12/18 angiosarcoma<br>lung cancer<br>brain cancer<br>subcohort: ever exposed to VC (n = 3,635)<br>liver cancer | SMR (90% CI)<br>3.00 (1.96-4.49)<br>1.23 (1.04-1.42)<br>1.62 (1.00-2.50)<br><br>3.33 (2.02-5.21) |
| Cohort Ward et al. (2000) | 12,700 male workers in the vinyl chloride industry in four European countries | No data | 29 y (mean) /<br>until 1996 | primary liver cancer | 2.40 (1.80-3.14) |
| nested case-control study (control: 224 subjects without history of cancer) Mastrangelo et al. (2003) | workers selected from 543 claimants out of a cohort of 1,658 workers at an Italian vinyl chloride/PVC production plant (38 cases with histologically verified lung cancer) | (0) subjects with the least exposure to PVC dust; (1) compounding workers, never baggers; (2) PVC baggers with several jobs at once, date of specific job change not indicated; (3) PVC baggers with known length of job, for whom start and end dates were available. | no data /<br>no data | lung cancer<br>variable:<br>group (3)<br><br>≥3.6 y spent as bagger<br>over 33 y of age at onset of job<br>calendar year at onset of job:<br>before 1967<br><br>≥1967 | <br>OR<br>5.6 (2.03-16.3) p<0.001<br>7.15 (2.55-19.3) p<0.0001<br>7.70 (2.72-21.1) p<0.0001<br><br>4.79 (1.73-12.5) p<0.001<br><br>4.55 (1.38-13.6) p<0.001 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | time elapsed from onset of job till end of follow-up or death:<br>>20 y<br>≤20 y<br><br>year as bagger (smoking and age constant) | <br>3.76 (1.51-8.99)<br>11.4 (2.21-60.7); p<0.01<br>1.20 (1.08-1.35; p =0.001 |
| nested case control (control: unexposed persons from same plant) Wu et al. (1989) | workers from a PVC polymerization plant in the US employed between 1942 and 1974 ever exposed to PVC dust | no, minimal, moderate, occasional peak, high and intimate exposure (not quantified) | ≤32 y / untill 31 Dec 1986 | liver cancer (16 cases, 81 controls)<br>brain cancer (13 cases, 62 controls)<br>lung cancer (98 cases, 456 controls) | OR not stat. sign. different from 1.00 |
| case-control study (control: male Swedish population; n =315) Hardell et al. (1997); Ohlson and Hardell (2000) | patients with testicular cancer and 30-75 years old from Swedish Cancer Registry between 1989 and 1992 (148 cases) | | 11-35 years latency<br>• low and high exposure combined<br>• low exposure | testicular cancer<br>(7 cases/ 2 controls)<br><br>(3 cases/2 controls) | OR<br>6.6 (1.4-32)<br><br>2.6 (0.3-3.2)<br>(not clear if 1 or 5 year latency period) |
| case-control study (control: male Swedish population; age- matched; n = 791) Hardell et al. (2004) | patients with testicular cancer (only germ cell tumours) and 20-75 years old from Swedish Cancer Registry between 1993 and 1997 (791 cases) | every work task was classified according to type of PVC contact with regards to dust levels | no data / no data | testicular cancer<br>>1 y latency<br>>10 y latency | OR<br>1.35 (1.06-1.71)<br>1.45 (1.06-1.98). |
| nested case-control study (control: unexposed persons from same plant; n = 140) Selenskas et al. (1995) | employees died from pancreatic cancer and worked 7 months or more at New Jersey plant between 1946 and 1967 with at least one hourly job assignment (cases = 28) | • vinyl and polyethylene processing (9 cases; 40 controls)<br>• resin pulverizing (10 cases; 55 controls), and resins and varnish (5 cases; 32 controls)<br>• sub-department vinyl and polyethylene processing[a] (8 cases and 34 controls) | >16 y / no data<br><br><br>>18 y (4 cases, 6 controls) | pancreatic cancer | 7.15 (1.28-40.1); p<0.05<br><br>no increased risk<br><br>8.98 (0.90-98.8) |

| | | | | | |
|---|---|---|---|---|---|
| cross-sectional mortality study (control: workers matched for age (and company, if possible); n = 134) Chiazze et al. (1980) | white women employees from 5 PVC fabricators (44 cases) | no, improbable, possible, definite and unknown exposure to PVC | no data / none | breast cancer | RR: all 4 exposure categories vs no exposure: 1.94 (CI not given; not significant) |
| "case-comparand" control: matched for age at diagnosis, sex, race, and county of residence Waxweiler et al. (1981) | 27 white male workers from above cohort | no data | no data / till 31 Dec 1973 | cancer of respiratory system:<br>• adenocarcinoma<br>• large cell undifferentiated | SMR<br><br>1.38; p not given<br>4.41; p not given |
| proportional mortality study IARC (1979) | male plastic workers (n = 707) died in 1970-1972 | no data | no data / no data | stomach cancer | O/E: 24/16.4; $p<0.05$) |
| proportional mortality study (control: US mortality) Chiazze and Ference (1981) | white employees from 17 PVC fabricators during 1964-1973 | no data | no data / no data | all cancers<br><br>digestive system cancer<br>urinary cancer<br>breast cancer<br>other unspecified cancers | PMR ($p = 0.05$)<br>male 1.16; female 1.30<br>male 1.27; female 1.48<br>female 2.84<br>female 1.34<br>male 1.60; female 1.96 |

[a] comprises: vinyl rigid; vinyl rigid planished; rigid vinyl liquid molding compounds; vinyl granular; vinyl fabrication; vinyl flexible, calendered; polyethylene fabrication.

Annex **G**

# Animal studies

| species / sex (no./group) | dose | freq | $X_{po}$ / $X_{pe}$ | no. survivors | no. animals with tumours | comments/specified skin tumours unless stated otherwise | Ref. |
|---|---|---|---|---|---|---|---|
| *Implant (subcutaneous, intrapleural)* | | | | | | | |
| rat Wistar sex not specified (45) | implant in abdominal wall of square or disc of commercial PVC known to contain some additives (0.04 mm thick and 15 mm wide) | once | 189-727 days / 189-727 days | at appearance of first tumour: 44 animals still alive | 17 malignant tumours at site after 189-727 days | fibrosarcomas and 1 liposarcoma (a similar but perforated film: 0/27 local tumours; sc implant of cotton: 0/50 local tumours); preliminary reporting and final results never reported | Oppenheimer et al., 1952/55 in IARC (1979) |
| rat Wistar sex not specified (similar group) | implant in abdominal wall of pure PVC film (0.03 mm thick) | once | 533 days / 533 days | not indicated | 4 malignant tumours | preliminary reporting and final results were never forthcoming | Oppenheimer et al. (1952/55) in IARC (1979) |
| rat Wistar M/F (35; control 25 rats) | implant into abdomen of PVC film 4x5x0.16 mm; control implant of glass of similar size | once | 800 days / 800 days | after 300 days: 20/30 and 30/35 | after 580 days: 0/30 and 2/35 | one sarcoma and one fibroma in PVC-treated rats | Russell et al. (1959) in IARC (1979) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| rat<br>strain not specified<br>not specified | PVC capsules, whole PVC films or perforated PVC films implanted in kidney | once | not specified<br>not specified | not specified | 5/16, 2/5 and 1/5 for PVC capsules, whole PVC films or perforated PVC films | sarcomas | Kogan and Tugarinova (1959) cited in IARC (1979) |
| rat<br>albino<br>sex not specified (80) | implants (of unstated size) of PVC film by laparotomy to surround the kidney | once | 3, 10, 15, 30, 90, 195, 285, 300 and 380 days<br>380 days | not specified | see comments | of rats that survived 285-375 days, 6/16 developed fibrosarcomas at site of implantation | Raikhlin and Kogan (1961) cited in IARC (1979) |
| rat<br>Wistar<br>M/F (24/sex) | inoculated intrapleurally with 20 mg PVC dispersion polymer in saline; controls: 20 mg UICC crocidolite, Min-U-Sil (quartz) in saline or saline | once | lifetime<br>lifetime | 12-18 months: 39/48 PVC | 6/24 PVC | 5 tumours of the liver and 1 tumour originating from site of inoculation: poorly differentiated sarcomas (3 possibly of Kupffer cell origin); none of animals with PVC after 18 months nor any of control animals developed this type of tumour; a new study with commercial dispersion polymer produced no tumours within 18 months (information limited to the above; study ongoing and final results never reported) | Wagner and Johnson (1981) |
| rat<br>Wistar<br>M/F (20/sex (control 12/ sex)) | 0 or one of three plasticizes PVCs (PVC-1, -2 and -3), subcutaneous implant in interscapular region of 10-20 mm piece, 0.3-0.5 mm thick | once | 2 years<br>2 years | not specified | Control: 8/ 10 M and 5/12 F; PVC-1: 11/17 M and 10/20 F; PVC-2: 12/15 M and 13/20 F; PVC-3: 13/18 M and 16/20 F | subcutaneous tumours (mostly malignant fibrous histiocytomas) at implantation site: Control: none; PVC-1: 3 M and 5 F; PVC-2: 5 M and 6 F; PVC-3: 8 M and 13 F; polyhydroxyethyl methacrylate had similar amount of subcutaneous tumours and dimethyl polysiloxane also showed some subcutaneous tumours | Maekawa (1984) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| rat<br>Fisher<br>F (12) | subcutaneous implant of PVC[a] (10x20x0.3 mm) in lateral abdominal region (2x) and on back | once | 741 days<br>741 days | not specified | 6/11 | seven subcutaneous tumours (similar morphological characteristics to human malignant fibrous histiocytoma) at site appearing 85 weeks after implantation; author concludes extremely high incidence of tumours compared to controls from a previous study | Hatanaka (1993) |
| rat<br>Sprague-Dawley<br>M (10) | subcutaneous implant of bulk PVC on 1 side of vertebral column or intramuscular with nanoparticles on contralateral side[b] | once | 6(4) or 12 (6) months<br>12 months | all animals | none | | Hansen et al. (2006) |
| *Intraperitoneal injection* | | | | | | | |
| rat<br>Wistar<br>F (51; control 102) | 0 or 500 (5x100) mg granular PVC[c] (particle size: 90% < 2.5 µm) in saline; ip injection | weekly | 5 weeks<br>28 months | 29 and 14 for control and treated, resp. | 2/102 and 5/51 for control and treated, resp. | preliminary results, final results never reported; average lifespan similar to control; author concludes no clear carcinogenic effect | Pott et al. (1987) |

[a] 4 groups with other materials were investigated.
[b] ratio of surface area to volume ($mm^{-1}$): 4.2 for bulk and $5x10^4$ for nanoparticles (50-60 mg).
[c] PVC was administered as one of 50 dusts in this study in order to say something on the relation between length, diameter and biopersistence and tumour incidence.

Abbrevations used: M= male; F= female; mg = milligramme; mm = millimeter; µm = micrometer; freq= frequency; $X_{po}$ = duration of exposure; $X_{pe}$ = duration of the experiment; bw = body weight; no. = number.

Annex **H**

# Carcinogenic classification of substances by the Committee

The Committee expresses its conclusions in the form of standard phrases:

| Category | Judgement of the committee ($GR_{GHS}$) | Comparable with EU Category | |
|---|---|---|---|
| | | 67/548/EEC (before 12/16/2008 | EC No 1272/2008 (as from 12/16/2008 |
| 1A | The compound is known to be carcinogenic to humans.<br>• It acts by a stochastic genotoxic mechanism.<br>• It acts by a non-stochastic genotoxic mechanism.<br>• It acts by a non-genotoxic mechanism.<br>• Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic. | 1 | 1A |
| 1B | The compound is presumed to be as carcinogenic to humans.<br>• It acts by a stochastic genotoxic mechanism.<br>• It acts by a non-stochastic genotoxic mechanism.<br>• It acts by a non-genotoxic mechanism.<br>• Its potential genotoxicity has been insufficiently investigated. Therefore, it is unclear whether the compound is genotoxic. | 2 | 1B |
| 2 | The compound is suspected to be carcinogenic to man. | 3 | 2 |
| (3) | The available data are insufficient to evaluate the carcinogenic properties of the compound. | Not applicable | Not applicable |
| (4) | The compound is probably not carcinogenic to man. | Not applicable | Not applicable |

Source: Health Council of the Netherlands. Guideline to the classification of carcinogenic compounds. The Hague: Health Council of the Netherlands, 2010; publication no. A10/07E.[23]

## Health Council of the Netherlands

### Advisory Reports

The Health Council's task is to advise ministers and parliament on issues in the field of public health. Most of the advisory opinions that the Council produces every year are prepared at the request of one of the ministers.

In addition, the Health Council issues unsolicited advice that has an 'alerting' function. In some cases, such an alerting report leads to a minister requesting further advice on the subject.

### Areas of activity

**Optimum healthcare**
What is the optimum result of cure and care in view of the risks and opportunities?

**Prevention**
Which forms of prevention can help realise significant health benefits?

**Healthy nutrition**
Which foods promote good health and which carry certain health risks?

**Environmental health**
Which environmental influences could have a positive or negative effect on health?

**Healthy working conditions**
How can employees be protected against working conditions that could harm their health?

**Innovation and the knowledge infrastructure**
Before we can harvest knowledge in the field of healthcare, we first need to ensure that the right seeds are sown.

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