Genotoxicity and Carcinogenicity of Ethylene Dichloride (EDC)

A Critical Assessment

submitted by the

Industry Consortium for EDC – subcommittee on Toxicology

(members: BASF, DOW, EVONIK, INOVYN, SHIN-ETSU, VYNOVA)

26 September 2018

Introduction

Ethylene dichloride (EDC; CAS # 107-06-2) is a high production volume industrial chemical primarily used in the manufacture of vinyl chloride. The toxicity of EDC has been extensively investigated over the past several decades. This includes investigations on the genotoxicity and carcinogenicity of EDC, which are the subject of this document.

Genotoxicity Data on EDC:

EDC has an extensive database on mutagenicity; the great majority of the studies are rather old and have not been conducted according to modern guidelines.

In a recent overview, Gwinn et al. (2011) reviewed the literature on the genotoxicity of EDC and concluded that "EDC exposure, in the presence of key enzymes (including CYP450s and/or GSTs), leads to DNA adduct formation, gene mutations and chromosomal aberrations." This is a valid conclusion insofar as the data from *in vitro* assay systems is concerned. There are compelling data in support of all the key events along the pathway to the induction of gene and chromosomal mutations *in vitro*. For example, there are multiple studies demonstrating DNA and protein adducts in bacterial and mammalian cells. In *vitro*, EDC induced DNA strand breaks in a comet assay as well as DNA repair synthesis in hepatocyte cultures. In terms of apical effects, EDC induced reverse mutations in bacteria cells in multiple studies. In mammalian cell cultures, EDC was shown to induce forward gene mutations, chromosomal aberrations and micronuclei with a low effective concentration of 1 mM for gene mutations (Tan and Hsie, 1981) and micronuclei (Doherty et al., 1996).

Concerning *in vivo* test systems, the conclusion drawn by Gwinn et al. (2011) that EDC induced gene mutations and chromosomal aberrations is not considered to be valid. In *vivo*, EDC does indeed induce a number of key events along the pathway to gene mutations and chromosomal aberrations; however, the available data do not provide evidence for apical effects themselves. EDC is readily absorbed and distributed to various tissue compartments following multiple routes of exposure (dermal, oral and inhalation). In addition, EDC-specific DNA and protein adducts have been demonstrated in multiple tissues following *in vivo* exposures. Thus, EDC is bioavailable and it (or its metabolites) can reach DNA to initiate the key molecular event responsible for the induction of the apical effects. The observation of DNA strand breaks indicates that cells experience genotoxic stress following *in vivo* EDC exposure. The available data indicates that EDC does not induce mitogenic or regenerative cell proliferation *in vivo*. This observation suggests that in tissues where the cells are not actively dividing (e.g., liver), a key component for the fixation of DNA damage into mutations is lacking. Negative results for mutation induction in the livers of a transgenic MutaMouse study are consistent with the above conclusion (Hachiya and Motohashi, 2000).

A recently conducted COMET assay in mammary gland cells (the target organ for carcinogenicity) after *in vivo* exposure of female rats to 200 ppm 1,2-dichloroehane for 4 weeks was clearly negative (Hotchkiss *et al*, 2014).

Several peripheral blood erythrocyte micronucleus tests in mice reported negative results following EDC exposure by inhalation (Armstrong and Galloway. 1993) or oral gavage (NTP, 1993). Since the target tissue for the endpoint scored in the above assays is the bone marrow, the negative results seem to indicate that the extent of EDC-induced DNA damage *in vivo* is not high or adequate to lead to detectable increase in chromosomal damage.

Results of a recent *in vivo* study reported by Lone et al (2016) seem to be an exception to the negative *in vivo* studies. However, in this study, EDC was administered by intraperitoneal injection to male Wistar rats which is not a relevant route of exposure for human hazard and risk assessment. In addition, there are too many inconsistencies and apparent errors in the reporting of the methods and results, which makes it difficult to accept the study findings and conclusions at face value. For example, the authors state that the animals were "…..divided by stratified randomization into 5 groups, each comprising of 5 male animals…" However, an examination of the study design presented in the results show that there are actually 15 groups (5 different treatments and 3 sacrifice times) instead of the stated 5 groups. The presentation of results is equally confusing as exemplified in Table 1 of their paper copied below:

Table 1. Micronuclei induction in polychromatic erythrocytes observed in the bone marrow cells of *Rattus norvegicus* treated *in vivo* with different doses of dichloroethane at various durations.

Group & dose	Time (h)	Total PCEs scored	Total number of MNPCEs	Mean frequency of MN per 1000 PCEs ± S.E.	P/N ratio
Normal control (NC)	24	2010	2	0.67 ± 0.33	0.796 ± 0.04
	48	2031	1	0.37 ± 0.31	0.784 ± 0.03
	72	2024	1	0.37 ± 0.30	0.789 ± 0.04
Positive control (PC) (40 mg/kg b. wt.)	24	2031	24	8.01 ± 1.73**	0.507 ± 0.01*
	48	2039	16	5.33 ± 1.45*	0.514 ± 0.00*
	72	2024	14	4.66 ± 2.33*	0.509 ± 0.01*
EDC I (80.7 mg/kg b.wt.)	24	2064	12	4.01 ± 1.15*	0.701 ± 0.03*
	48	2039	8	2.67 ± 1.20**	0.754 ± 0.02**
	72	2139	7	2.33 ± 1.31*	0.739 ± 0.02**
EDCII (161.4 mg/kg b.wt.)	24	2133	15	5.00 ± 1.73**	0.691 ± 0.02**
	48	2191	13	4.33 ± 1.76**	0.699 ± 0.03
	72	2164	10	3.34 ± 1.85*	0.684 ± 0.01**
EDCIII (242.1 mg/kg b.wt.)	24	2039	17	5.67 ± 1.45**	0.614 ± 0.02**
	48	2043	14	4.66 ± 1.85**	0.622 ± 0.01**
	72	2012	11	3.67 ± 1.76**	0.637 ± 0.04*

Normal control (water); positive control (cyclophosphamide); EDC I (80.7 mg/kg b.wt); EDC II (161.4 mg/kg b.wt); EDC III (242.1 mg/kg b.wt);PCEs (Polychromatic erythrocytes); MNPCEs (micronucleated polychromatic erythrocytes); *statistically significant values at.
*$p<0.05$, **$p<0.01$, ***$p<0.001$*(One way ANOVA, post hoc Tukey).*

In the methods section, the authors state that they have scored 2000 PCEs per animal; however, the total PCEs scored was listed as approximately 2000 in the above table. Does

this mean that they only had one animal for each time point? Equally confusing is the derivation of mean frequency of MN per 1000 PCEs in the above table. For example, the 24 hour normal control had 2 MNPCEs for a total PCEs scored of 2010. It is beyond simple comprehension as to how the authors were able to calculate a mean frequency of 0.67 MN per 1000 PCE for this group. Similar challenges exist for other calculations in this table as well as for calculations in other tables. The methods section are either incomplete or inaccurate and the values in the table are incomprehensible. Without having access to the raw data, it is difficult to place any credence to the purported positive findings reported for all genotoxicity endpoints at all dose levels and at each sampling time.

In summing up the *in vivo* data, it is reasonable to conclude that EDC is capable of inducing the indicator or precursor events along the pathway to gene mutations and chromosomal aberrations. However, data from reliable studies do not indicate that EDC has the ability to induce gene mutations or chromosomal aberrations *in vivo*.

When *in vitro* and *in vivo* data are taken together, one may assume that EDC has the potential to be a mutagen and/or a clastogen under certain experimental conditions. The strength of evidence for its mutagenic potential *in vitro* is rather strong. As stated earlier, while EDC has the potential to be an *in vivo* mutagen, evidence for such an activity is lacking.

Possible Reasons for Discordant In Vitro Vs. In Vivo Results:

While there are many reasons for divergence between *in vitro* and *in vivo* test results (such as the idiosyncrasies of *in vitro* test systems), one possible scenario could be that the concentrations necessary to induce the apical effects are not attainable *in vivo*. As stated earlier, the lowest effective concentration for the induction of gene mutations and micronuclei *in vitro* was 1 mM (equivalent to 100 µg/mL). The highest dose tested in the MutaMouse gene mutation assay was 150 mg/kg, single oral dose. The dose level tested in the *in vivo* micronucleus test by Amrmstrong and Galloway (1997) was also 150 mg/kg/day for up 41 wks. At this dose levels, the peak blood concentration of EDC was expected to be approximately 70 µg/mL (OECD SIDS, 2002), a value similar to the minimum effective concentration of 100 µg/mL for the induction of gene mutations and micronuclei *in vitro*. Thus, it is unlikely that failure to attain adequate systemic concentration of EDC was responsible for the negative results observed *in vivo* for the apical endpoints.

Another reason for discordant *in vitro* vs. *in vivo* results is the use of inadequate or sub-optimal protocols for the *in vivo* studies. Neither the MutaMouse gene mutation assay nor the erythrocyte micronucleus test on EDC is compliant to the current OECD guidelines for the conduct of these assays. For the MutaMouse study, the deviations include inadequate dose level selection, fewer numbers of animals at each dose level, and failure to include a rapidly proliferating tissue such as the bone marrow for mutation analysis. For the micronucleus studies, there are a number of guideline deviations such as the scoring of normochromatic erythrocytes, rather than polychromatic erythrocytes for micronuclei and inadequate number

of cells enumerated for the endpoint. Thus, it is likely that the protocols used for the *in vivo* assays on EDC did not have the adequate power to detect an effect on the apical endpoints.

Conclusions on the genotoxicity of EDC:

Overall, a critical assessment of the available genotoxicity data on EDC leads to the conclusion that its *in vivo* mutagenicity is an open question. While this substance might be an *in vivo* mutagen, there are no data to support or refute this assumption.

Carcinogenicity of EDC and Mode of Action:

EDC has been shown to induce tumors in rats and mice by oral and inhalation routes of exposure. In the rat inhalation carcinogenicity study of Nagano et al. (2006), EDC (0, 10, 40 or 160 ppm) induced dose-dependent increase in subcutaneous fibroma, mammary gland tumors and peritoneal mesotheliomas (males only); only mammary gland tumors at the highest dose were identified to be significantly different from the concurrent controls. In mice, inhalation exposure to EDC (0, 10, 30, or 90 ppm) produced a dose-dependent increase in lung, mammary, liver and endometrial tumors in females; none of these tumor types was significantly different from the concurrent controls (Nagano et al., 2006).

In the oral gavage carcinogenicity studies (NCI, 1978), there was a statistically significant positive association between EDC dosage and the incidence of squamous-cell carcinomas of the forestomach and haemangiosarcomas of the circulatory system in the male rats. In addition, a significantly increased incidence of adenocarcinomas of the mammary gland was also observed in female rats. In the NCI mouse gavage study, the tumor target tissues were mammary gland, endometrium, and the lungs in females and only lungs in males.

Mode of Action for Mammary Tumours

The potential mode of action for rat mammary tumours was recently investigated in female F344/DuCrlvrats, which were exposed to target concentrations of 0 or 200 ppm of DCE vapours (6 hours/day, 7 days/week) for at least 28 exposures (Hotchkiss *et al*, 2014). The parameters measured in this study included – besides the common parameters in a repeated dose study - serum prolactin levels, measurement of reduced (GSH) and oxidized (GSSG) glutathione, DCE-glutathione conjugates, DNA adducts in mammary and liver tissue, a Comet assay and cell proliferation in mammary tissue, and histopathologic and morphometric evaluation of mammary gland structure.

The results of this study were as follows:

- Repeated inhalation exposure to 200 ppm vapour for 4 weeks had no effect on body weights, clinical observations, serum prolactin levels, mammary epithelial cell proliferation, or mammary gland morphology or histopathology.
- Clear evidence of target tissue exposure with quantifiable levels of the biomarker adduct S-(2-guanylethyl) glutathione (GEG) present in liver and mammary tissue from EDC-exposed rats, but not in controls.
- No exposure-related DNA damage was detected in the Comet assay with mammary epithelial cells isolated from EDC-exposed rats.
- EDC exposure had also no effect on GSH or GSSG levels in mammary tissue.
- No glutathione conjugates (HESG or EBG) were measured at levels greater than the lower limit of quantitation in mammary or liver tissue samples.
- DCE exposure had no effect on DNA adduct levels (8-OHdG) in mammary tissue.

In conclusion, repeated inhalation exposure to 200 ppm DCE vapor, a concentration approximately 20% higher than the concentration reported to induce mammary tumors in rats (Nagano et al., 2006) had no statistically significant effect on serum prolactin levels, GSH/GSSG levels, cell proliferation, or DNA damage in mammary tissue. The results of this sub-acute inhalation-exposure study do not support a specific known Mode of Action for DCE-induced mammary tumors in rats. In particular, the lack of any exposure-related genotoxic effects in the Comet assay or relevant target-tissue specific DNA adducts does not support a genotoxic mode of action.

Therefore, the EDC consortium does not agree with the position of DECOS that EDC "is a stochastic genotoxic carcinogen".

Derivation of a Safe Level for Workers

The suspected relationship between the carcinogenic response of EDC and the associated risk has been carefully considered in industry's evaluation. Therefore, the EDC consortium proposes DECOS to take the following key facts into consideration:

- There is one long-term inhalation study with EDC (in rats and mice) available in which mammary tumours were observed in rats.
- These findings were not confirmed in two other long-term inhalation studies.
- Based on a weight of evidence approach, EDC is not considered to be mutagenic *in vivo*.
- A recent, well-conducted Mode of Action study indicates that there is no support for a non-threshold mechanism for the induction of mammary tumours.
- In particular, no exposure-related genotoxic effects (Comet assay) were observed in target mammary epithelial cells after repeated *in vivo* inhalation exposure of female rats.
- Finally, epidemiological data are not supportive of EDC exerting a carcinogenic effect in humans.

The industry proposes DECOS to take into consideration whether a threshold approach could be used as a valid alternative to the proposed approach to consider EDC a "stochastic genotoxic carcinogen", which leaves questions about the validity of its justification due to the remaining uncertainties regarding the Mode of Action.

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Beschouwing van Ariane Gennissen, bedrijfsarts ten behoeve van Shin-Etsu aangaande Draft 1,2-Dichloroethane Health-based recommendation on occupational exposure limits van DECOS 2018. (informatie die niet eerder door het REACH EDC Consortium bij DECOS is aangeleverd)

De Gezondheidsraad heeft de selectie van de studie voor Cancer Risk Derivation beter onderbouwd dan dat SCOEL dat eerder heeft gedaan. De uiteindelijke keuze van de Gezondheidsraad voor de incidentie adenocarcinomen bij de vrouwelijke muizen van de inhalatiestudie van Nagano is dientengevolge beter navolgbaar en logischer dan de uiteindelijke keuze van SCOEL (te weten incidentie adenocarcinomen gecombineerd met fibroadenomen bij de vrouwelijke ratten uit dezelfde inhalatiestudie).

Het hele draftrapport is informatief en helder; ik adviseer Shin-Etsu (naast de reactie vanuit het REACH EDC-Consortium) slechts één opmerking aangaande de kinetiek en metabolisme aan te dragen.

De GR schrijft in paragraaf 2.2.1 Kinetics and metabolism:

> *While activation of 1,2-dichloroethane through the oxidation pathway (by CYP450) may play a role in chromosomal aberrations, the glutathione conjugation pathway leading appears to be the predominant 1,2-dichloroethane mutagenicity pathway.*

Een volgende aanvulling op deze tekst lijkt mij wenselijk:

Bij lage uptake van 1,2-dichloorethaan is bekend dat de oxidatieve CytochroomP450-pathway veruit de voornaamste pathway is (vanwege de hoge affiniteit). De directe GSH-conjugatiepathway wordt in een organisme pas dominant als de oxidatieve CytochroomP450-pathway bezig is te verzadigen (vanwege lage affiniteit doch hoge capaciteit, uitleg blz. 22 SCOEL rapport). Bij muizen is het punt van metabole verzadiging voor zover ik weet niet bekend, maar bij ratten is door Gwinn et al afgeleid dat metabole verzadiging van de oxidatieve CytochroomP450-pathway (pas) wordt bereikt bij een inhalatoire blootstelling van ongeveer 150 ppm aan 1,2-dichloorethaan (Gwinn MR, Johns DO, Bateson TF, Guyton KZ. A review of the genotoxicity of 18 1,2-dichloroethane (EDC). Mutat Res 2011; 727(1-2): 42-53).

Waarom is deze aanvulling m.i. relevant?

De volgende incidentiecijfers (tabel 5 uit draftrapport DECOS) aanschouwend:

Dose (mg/m3)	Number of female mice per dose	Number of female mice with mammary gland adenocarcinoma
0	49	1
40	50	2
120	50	1
360	50	6

bestaat de mogelijkheid dat de hoogte van benodigde concentratie voor de metabole verzading van de oxidatieve CytochroomP450-pathway ook bij deze populatie een rol speelt, resulterend in de vlakke dosis respons curve bij doses 0, 40 en 120 mg/m3 en de significante responsstijging bij de dosis van 360 mg/m3.

De GR schat het risico voor de mens en zij berekent risicogetallen volgens de methodiek beschreven in Gezondheidsraad Leidraad berekening risicogetallen voor carcinogene stoffen. (Den Haag, 2012; Publicatie no. 2012/16) in paragraaf 4.4:

> *Stap 4: Het schatten van het risico voor de mens en het berekenen van risicogetallen.*
>
> *In de praktijk zal de in een dierproef bepaalde maat voor de carcinogeniteit van een stof vele ordes van grootte hoger liggen dan het effect dat ten grondslag ligt aan het risicogetal (namelijk het effect dat geassocieerd is met een extra risico van 4 x 10-3 of 4 x 10-5). Aangezien over het verloop van de dosis-responscurve in dit lage gebied zelden betrouwbare informatie voorhanden is, zal de commissie lineair moeten extrapoleren bij de berekening van een risicogetal.*
>
> *Slechts als de relatie tussen blootstelling en effect in het lage dosisgebied niet lineair blijkt te zijn, kan een andere manier van extrapolatie gehanteerd worden. Dit moet dan wel ondersteund worden door de beschikbare (mechanistische) gegevens.*

Men kan zich afvragen of bij toepassen van lineaire extrapolatie vanuit de gegevens van de huidige drie beschikbare meetgroepen (vier inclusief de controlegroep) het effect van een (mechanistisch te verklaren) kleinere hellingshoek bij lage blootstellingen ten opzichte van een grotere hellingshoek bij hoge blootstellingen voldoende in de redenering en conclusies mee wordt gewogen.

Comments BOHS on the 1,2-dichloroethane DECOS document

Comments prepared by expert John Cherrie, BHOS
Wednesday, 17 August 2016

1,2-dichloroethane has been classified by the International Agency for Research on Cancer (IARC) as possibly carcinogenic to humans based on limited human epidemiological data and sufficient animal toxicity (IARC category 2b). The data presented in the DECOS document does not suggest that this position has importantly changed, i.e. there is still doubt about the carcinogenic potential of the compound in humans.

The document provides a toxicological assessment of the possible risk from a working lifetime (40-years) of daily exposure. I am not really able to comment authoritatively on the calculations or the selection of the key study for the assessment. However, it seems as though the justification for the study by Nagano et al is rather weak:

"…the increase in mammary gland adenocarcinomas was not statistically significant compared to concurrent controls, the incidences exhibited a statistically significant positive trend and the maximum incidence in historical controls was exceeded. Therefore, the Committee considers the slight increase in the incidence of mammary gland adenocarcinomas biologically significant and related to treatment. The mouse study was selected for cancer risk derivation, because the mice developed mammary tumours at a lower exposure level than the rat."

There are only 6 mammary gland adenocarcinomas in the mice and it's hardly a convincing dose-response relationship (see table on next page). Also, from a paper by Russo (attached): "Spontaneous mammary tumors are frequently observed in long-term rodent studies. In mice, the development of ''spontaneous'' mammary tumors is linked to the infection of female mice with either an exogenous mouse mammary tumor virus (MMTV) or a less virulent endogenous provirus…". The number of tumours identified by Nagano et al was just a little above the maximum in the historic control data (4 in 50 animals in the controls vs 6 in 50 in these tests). Also Russo states "…the utilization of experimental models of mammary carcinogenesis in risk assessment requires that the influence of ovarian, pituitary, and placental hormones, among others, as well as overall reproductive events are taken into consideration, since they are important modifiers of the susceptibility of the organ to neoplastic development."

However, as I've written these are the observations of a hygienist not a toxicologist.

Table 2. Number of tumor-bearing mice of both sexes exposed by inhalation to DCE or clean air for 2 yr

(A) Male

Group Name	Control	10 ppm	30 ppm	90 ppm	Peto's	JBRC historical control data	
Number of animals	50	49[a)]	50	50	test	Incidence[b)]	Min.–Max.[c)]
	(%)	(%)	(%)	(%)		(%)	(%)
Liver							
Hemangiosarcoma	0	4	6*	5*		27/748	0/50 – 5/50
	(0.0)	(8.2)	(12.0)	(10.0)		(3.6)	(0.0 – 10.0)

(B) Female

Group Name	Control	10 ppm	30 ppm	90 ppm	Peto's	JBRC historical control data	
Number of animals	49[a)]	50	50	50	test	Incidence[b)]	Min.–Max.[c)]
	(%)	(%)	(%)	(%)		(%)	(%)
Lung							
Bronchiolo-alveolar adenoma	4	1	3	8	↑	29/749	0/50 – 5/50
	(8.2)	(2.0)	(6.0)	(16.0)		(3.9)	(0.0 – 10.0)
Bronchiolo-alveolar carcinoma	1	0	1	3	↑	21/749	0/50 – 3/50
	(2.0)	(0.0)	(2.0)	(6.0)		(2.8)	(0.0 – 6.0)
Combined bronchiolo-alveolar adenoma	5	1	4	11	↑↑	49/749	0/50 – 6/50
and bronchiolo-alveolar carcinoma	(10.2)	(2.0)	(8.0)	(22.0)		(6.5)	(0.0 – 12.0)
Uterus							
Endometrial stromal polyp	2	0	1	6	↑↑	26/748	0/50 – 4/50
	(4.1)	(0.0)	(2.0)	(12.0)		(3.5)	(0.0 – 8.0)
Mammary gland							
Adenocarcinoma	1	2	1	6	↑↑	20/749	0/50 – 4/50
	(2.0)	(4.0)	(2.0)	(12.0)		(2.7)	(0.0 – 8.0)

The more important issues from my perspective are how these data may be used in the setting of a limit value, which I accept is not the remit of the present report. Exposures in the PVC manufacturing industry in Europe are low. In 2006 the European plastics manufacturers carried out an extensive survey of 1,2-dichloroethane levels. A total of 1,653 eight-hour time-weighted average exposure measurements were taken across different manufacturing sites and job groups. Measured exposures ranged from 0.2 ppm to 10 ppm (0.8 – 40 mg/m^3) with an average exposure of 0.48 ppm (1.9 mg/m^3) across all job groups and sites. Based on these data about 11% of manufacturing workers were exposed to average levels above 1 ppm (4 mg/m^3) and only 0.36% of workers were exposed above 5 ppm (20 mg/m^3). Exposures have been decreasing have probably been decreasing over recent years by about 9% per annum.

Less than 3,000 people are potentially exposed in Europe, most in the manufacture of VCM with about 500 exposed when 1,2-dichloroethane is used as a solvent in the pharmaceutical industry. Based on the risk estimates from DECOS, if the exposed workers were all women and they were exposed throughout a working lifetime then it is still unlikely that any of them would have a cancer associated with their exposure, i.e. the risk from the average exposure in the industry is likely around 1 in 10,000.

We prepared a report on 1,2-dichloroethane for the EC, which may be helpful and I have attached a copy.

Comments prepared by expert Rhys Jones, BOHS

Mr R. Jones made several suggestions for improvements of the report. The comments he added to the draft report are presented in the table below.

SECTION & PARAGRAPH (of the first draft report)	COMMENT
Contents	I would consider adding a list of abbreviations at the beginning of the document... otherwise people have to look to the references at the end to find the abbreviations.
Executive summary 'the Dutch Expert 3 Committee on Occupational Safety (DECOS)' '…classified by the Health Council or the European Union in category 1A or 1B, 8 and of which are considered carcinogens acting by a stochastic genotoxic mechanism.'	Hereafter referred to as 'the Committee'? '... classified as category 1A or 1B carcinogens and considered to act via a stochastic genotoxic mechanism...'
1.1 Background '…occupational exposure limits…'	(OELs)
2.2.2 Human studies 'People accidently ingested 1,2-dichloroethane (15-60 ml) died within 10-28 hours of exposure.'	I would reword to 'accidental ingestion of 15-60mls of 1,2-dichloroethane has been reported to cause death within 10-28 hours of exposure'.
2.2.2 Human studies 'Repeated exposure in humans has been associated with various effects including respiratory and haematological effects.'	Repeated short-term acute exposures, or long-term chronic?
2.2.3 Animal studies *Acute toxicity* 'The LD50 for oral exposure ranged from 770-967 mg/kg bw in rats, 413-911 mg/kg bw 4 in mice, and approximately 910 mg/kg bw in rabbits….'	Could these be summarised in a table? It would make it clearer.
3.1 Human studies *Cohort studies* 'In a cohort of male employees…	Was any information given about age range, length of employment?

Comments on DECOS draft document on 1,2-Dichloroethane

By: Crystal D. Forester, Research Chemist,
NIOSH/National Personal Protective Technology Laboratory,
1095 Willowdale Road, Morgantown, WV 26505

SECTION & PARAGRAPH	COMMENT
Critical studies included?	**All critical studies have been presented and evaluated. The committee is commended for their thorough and systematic evaluation and elimination of studies which had significant limitations.**
Detail of critical studies adequate?	**Yes, sufficient detail was provided to support conclusions.**
Concise presentation of information?	**The information was presented in a concise manner with sufficient detail concerning the multiple studies described.**
Limitations of critical studies?	**The studies used for calculations had no limitations.**
Alternative interpretations of assessments?	**No, the data presented and used in the calculations supported the conclusions of the cancer risks.**
Specific Comments:	
Page 12: lines 9 & 37	**Remove the word "few" from sentences. If needed, use a more quantitative term.**