Bijlage C02:
- 1e RIVM rapport oktober 2010

Ministerie van Defensie

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Met de brief van 28 januari jl. (Kamerstuk 32 500 X, nr. 81) heb ik de Kamer geïnformeerd over de stand van zaken van het onderzoek naar de gevolgen van het gebruik van PX-10 bij Defensie. Het eerste deelonderzoek is voltooid en in overeenstemming met het verzoek van de vaste commissie voor Defensie van 1 april jl. (kenmerk 32500-X-89/2011D16955) bied ik u in bijlage een afschrift daarvan aan (RIVM-rapport 609037001/2010).

Het RIVM concludeert dat het onderzoek van het ministerie van Defensie naar behoren is uitgevoerd. Wel is het benzeengehalte van PX-10 volgens het RIVM ongeveer een factor 10 lager dan in het rapport is aangenomen. Voorts heeft het RIVM vastgesteld dat na de publicatie van het rapport nieuwe informatie beschikbaar is gekomen met beperkt bewijs dat de blootstelling aan benzeen naast acute myeloide leukemie (AML) ook andere kwaadaardige aandoeningen kan veroorzaken. Het betreft acute lymfatische leukemie (ALL), chronische lymfatische leukemie (CLL), multipel myeloom (MM) en, met een minder sterk verband, non-hodgkin lymfomen (NHL). Ook zijn enkele aanvullende gezondheidsrisico's van de blootstelling aan tolueen en xyleen benoemd.

De nieuwe informatie die het RIVM naar voren heeft gebracht is voor mij reden de criteria voor ondersteuning of voor een tegemoetkoming te verruimen. In de brief van 11 juni 2009 (Kamerstuk 31 700 X, nr. 120) was gemeld dat voor de aandoeningen acute myeloide leukemie (AML), myeloplastisch syndroom en aplastische anemie een causaal verband wordt aangenomen indien er sprake is geweest van beroepsmatig werken met benzeenhoudend PX-10. Voortaan zal hetzelfde gelden voor de aandoeningen acute lymfatische leukemie (ALL), chronische lymfatische leukemie (CLL), multipel myeloom (MM) en een van de vormen van non-hodgkin lymfoom, te weten folliculair lymfoom.

Om in aanmerking te komen voor een financiële tegemoetkoming of voor ondersteuning moet de (voormalig) defensiemedewerker ook voldoen aan de overige criteria die in de brief van 11 juni 2009 worden genoemd. Deze criteria betreffen risicofunctie, blootstelling aan benzeen en risicoperiode na blootstelling. Het criterium risicofunctie zal ruimhartig worden gehanteerd.

Het RIVM zal het tweede deel van het onderzoek vooral richten op de risicoschatting voor de aandoeningen waarvan het verband met benzeenhoudend PX-10 is vastgesteld. Voor andere gezondheidsrisico's door blootstelling aan PX-10 wordt in het RIVM-rapport dat als bijlage is gevoegd, uiteengezet dat een kwantitatieve risicobeoordeling waarschijnlijk niet mogelijk is.

DE MINISTER VAN DEFENSIE

drs J.S.J. Hillen

Rijksinstituut voor Volksgezondheid
en Milieu
*Ministerie van Volksgezondheid,
Welzijn en Sport*

Evaluatie van het PX-10 rapport van het ministerie van Defensie

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Delen uit deze publicatie mogen worden overgenomen op voorwaarde van bronvermelding: 'Rijksinstituut voor Volksgezondheid en Milieu (RIVM), de titel van de publicatie en het jaar van uitgave'.

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Rapport in het kort

Evaluatie van het PX-10 rapport van het ministerie van Defensie

In 2008 is het ministerie van Defensie aansprakelijk gesteld voor de gezondheidsschade die een ex-militair zou hebben opgelopen als gevolg van zijn werkzaamheden binnen de Koninklijke Marine, en in het bijzonder door het werken met het onderhoudsmiddel "PX-10". Daarna heeft het ministerie literatuuronderzoek uitgevoerd naar de mate waarin Defensiemedewerkers aan dit onderhoudsmiddel van (hand) vuurwapens zijn blootgesteld. Dit onderzoek is onlangs beoordeeld door het RIVM. Het RIVM heeft daarbij de hulp ingeschakeld van het Instute for Risk Assessment Sciences (IRAS). Dit instituut heeft specifieke kennis op het gebied van arbeidsepidemiologie.

Het RIVM en het IRAS concluderen dat het onderzoek van Defensie naar behoren is uitgevoerd. Wel schatten beide instituten de mate van blootstelling aan benzeen, een ingrediënt van PX-10, tien keer lager in dan Defensie. Ook geven de onderzoeksinstituten een aantal aanvullingen op de opsomming van mogelijk te verwachten gezondheidseffecten, voornamelijk op het gebied van bepaalde vormen van lymfeklierkanker. Om de mogelijke blootstelling beter in te schatten en vervolgens de mogelijke effecten te kunnen relateren aan de klachten is nader onderzoek noodzakelijk. Defensie heeft het onderhoudsmiddel PX-10 tot 1995 gebruikt.

PX-10, Wapenonderhoud, Benzeen

1 Inleiding

In 2008 is het ministerie van Defensie aansprakelijk gesteld voor de gezondheidsschade die een ex-militair van de Koninklijke Marine (KM) zou hebben opgelopen als gevolg van zijn werkzaamheden binnen de KM en in het bijzonder door het werken met het onderhoudsmiddel "PX-10".
Mede omdat dit onderhoudsmiddel "PX-10" in elk geval gedurende meerdere jaren benzeen, tolueen en xyleen bevatte, en daarnaast veelvuldig binnen de Defensieorganisatie werd gebruikt, heeft het ministerie van Defensie een onderzoek ingesteld naar "de samenstelling, het gebruik en de gezondheidseffecten van PX-10 op defensiepersoneel". Het doel van dit onderzoek is om zo objectief mogelijk te kunnen beoordelen of en in welke mate, (oud-) defensiemedewerkers extra gezondheidsrisico's hebben gelopen door het werken met het onderhoudsmiddel PX-10.

Het onderzoek bestaat uit 2 delen:

1) een door het ministerie van Defensie zelf uitgevoerd onderzoek naar de samenstelling, het gebruik, de gezondheidseffecten van PX-10 op defensiepersoneel en de nog openstaande vragen welke aan het RIVM moeten worden voorgelegd voor nader onderzoek.
2) Een extern onderzoek, uitbesteed aan het RIVM, waarin onder andere gevraagd wordt een oordeel te geven over de rapportage over het door het ministerie van Defensie zelf uitgevoerde onderzoek.

Het ministerie van Defensie heeft het RIVM gevraagd het tweede deel van het onderzoek uit te voeren omdat het instituut een aanzienlijke kennis op het gebied van de epidemiologie en de toxicologie heeft. Omdat bij dit onderzoek ook specifieke kennis op het gebied van arbeidsepidemiologie noodzakelijk is, heeft het RIVM samenwerking gezocht en gevonden bij het IRAS (Institute for Risk Assessment Sciences) van de Universiteit Utrecht. In verband met de ingewikkelde problemen rondom de blootstellingschattingen (van de samenstelling van PX-10 door de jaren heen is niet veel bekend) heeft het IRAS op zijn beurt intensief samengewerkt met het IOM (Institute of Occupational Medicine) uit het Verenigd Koninkrijk. Het voorliggende rapport is het resultaat van de samenwerking tussen IRAS en IOM, onder begeleiding van het RIVM.

Het externe RIVM/IRAS/IOM onderzoek betreft een drietal deelprojecten:

1. Het beoordelen van een door het ministerie van Defensie opgesteld rapport over de stand van zaken met betrekking tot PX-10 ten aanzien van:
    a. aannames die worden gedaan resp. conclusies die worden getrokken ten aanzien van exacte samenstelling van het product PX-10
    b. de conclusies uit de door het ministerie van Defensie uitgevoerde literatuurstudie naar gezondheidsrisico's van bestanddelen van PX-10
    c. de beschreven risicoscenario's voor hoog en laag risico.

2. Het (doen) uitvoeren van onderzoek waarmee de gezondheidsrisico's voor een hoog risicoscenario respectievelijk een laag risico scenario ingeschat kunnen worden voor in het verleden aan PX-10 blootgesteld defensiepersoneel. Dit onderzoek omvat zowel blootstellingsschattingen als gezondheidsrisicoschattingen
3. Het (doen) ontwikkelen van een methodiek om voor overige blootstellingscenario's de relatieve risico's van de blootstelling aan PX-10 in te kunnen schatten. De methodiek zal zodanig vormgegeven worden dat zij, na voldoende training, zelfstandig uitgevoerd kan worden door deskundigen (arbeidshygiënisten) van de defensie organisatie. Omdat in dit stadium nog niet duidelijk is hoe een stand alone tool voor de inschatting van blootstelling / gezondheidrisico's bij verschillende scenario's vorm gegeven kan worden en wat de vormgeving zal kosten valt deze specifieke deelvraag niet binnen de opdracht. Op basis van gebruikerswensen kan, wanneer de methodiek voor de twee reeds beschreven risicoscenario's is ontwikkeld, alsnog, indien gewenst, een aanvullende offerte opgesteld worden voor het ontwikkelen van deze stand alone tool.

Dit briefrapport beschrijft de resultaten van het eerste deelproject. Hierin is het door het ministerie van Defensie samengestelde rapport aangaande PX10 geëvalueerd door een team van wetenschappers van het IRAS en het IOM. In de evaluatie zijn de aannames en conclusies van het rapport getoetst ten opzichte van de huidige wetenschappelijke kennis omtrent PX10 en haar mogelijke bestandsdelen. Het door het IRAS en IOM opgestelde evaluatierapport is opgenomen in bijlage 1.

Het rapport van het ministerie van Defensie gaat in op de volgende vragen:

1. Kan meer duidelijkheid worden verkregen over de samenstelling van PX-10 door de jaren heen.
2. Kan meer duidelijkheid worden verkregen over het gebruik van PX-10 door de jaren heen.
3. Kan meer duidelijkheid worden gegeven over de extra gezondheidsrisico's die (oud)defensie medewerkers mogelijk hebben gelopen door het werken met PX-10.
4. Welke vragen moeten aan de civiele wetenschappelijk organisatie worden voorgelegd om nog openstaande vragen te kunnen beantwoorden.

In de evaluatie van het rapport ligt de nadruk op de nauwkeurigheid van de aannames en conclusies met betrekking tot de samenstelling, gebruik en gezondheidseffecten van PX-10.

2 Conclusie

De conclusie van de evaluatie is dat het rapport van het ministerie van Defensie in het algemeen in overeenstemming is met de huidige wetenschappelijke literatuur. Echter, het door het IRAS en IOM ingeschatte benzeengehalte van PX-10 ligt ongeveer een factor 10 lager dan de inschatting van het ministerie van Defensie. Ten aanzien van het gebruik van PX-10 is gebleken dat het lastig is om daar in deze fase

van het onderzoek uitspraken over te doen. Hier zal in aanvullende focusgroepbijeenkomsten aandacht aan besteed worden. Daarnaast geeft het evaluatierapport een aantal aanvullingen op de beschrijving van de gezondheidseffecten van PX-10, waaronder bepaalde vormen van kanker in relatie tot blootstelling aan benzeen (met name van de lymfeklieren) en effecten op de reproductie in relatie tot blootstelling aan oplosmiddelen. Om de door defensie gebruikte scenario's van hoge en lage blootstelling, gebaseerd op informatie over het gebruik van PX-10, te kunnen evalueren zijn eveneens aanvullende focusgroepbijeenkomsten nodig. Deze aanvullende bijeenkomsten zijn voorzien in de 2de fase van het onderzoek. Deze tweede fase zal aansluitend door het IRAS in samenwerking met het RIVM worden uitgevoerd.

Appendix 1: Rapportage IRAS

Evaluation of the internal report on PX-10 by the ministry of Defence

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1. Introduction

In 2008 the Ministry of Defence received a claim of an ex-military person regarding serious health complaints due to the use of PX-10. Subsequently, this claim has received attention by the national government, the military union and the media. As PX-10, at least for part of the time, contained benzene and other organic solvents the suggestion has been that the Ministry of Defence, although aware of the potential health effects, has not acted adequately in eliminating or reducing the exposure or in providing appropriate personal protection to their employees. In response, the Ministry of Defence has agreed to further investigate the use of PX-10, its contents and the potential associated health effects with the goal to objectively assess the potential health risks that (ex-) military personnel might have had due to the historical use of PX-10. As part of this investigation the Ministry of Defence has produced an internal report in which four main questions were addressed (Neuteboom et al. 2009):

1. What was the composition of PX-10 over time?
2. How was PX-10 used over time?
3. What is known about the possible (additional) health effects that defence personnel might have had due to the use of PX-10?
4. Which questions need to be answered by scientific organisations in order to answer open questions?

In this evaluation of the internal report of the Ministry of Defence we will focus on the accuracy of the assumptions and conclusions made with regard to the composition, use and related health effects of PX-10.

2. What was the composition of PX-10 over time?

The report states that the main components of PX-10 were white spirit (85 – 95%), mineral oils (1-12%) and additives (1.5 – 6%). The conclusion that white spirit is likely the main constituent of PX-10 seems consistent with the physical properties described for PX-10.

Several historical safety data sheets of PX-10 by the Dutch ministry of defence are available. Table 1 shows the information available for the different years based on the safety data sheets. These sources describe roughly the composition of PX-10 after 1987, and in the transition time around the year 1984-1985. However, older documents are less explicit and cannot be dated exactly. The wording of the main content changed over the years from "turpentine" to "naphta".

Table 1. Sources of information about the content of PX-10

Year	PX-10 content description	References
<1985	Turpentine* 93% (max .20% aromatic) mineral oil 1 % additives 6 %	(1) (2)
1984-1985	Turpentine* 85 - 95% (max. 20% aromatic), mineral oil 3 - 12%, fatty esters 0,5 - 1,5% additives 1,5 - 2,5%	(3)
>1987	Naphta 90% (max. 1% aromatic of which 0.0005% benzene), mineral oil 7%, fatty esters 1%, other components 2%.	(4)

* Turpentine is a translation of the Dutch word 'Terpentine' which is used for several solvent mixtures among which white spirit

(1) Defensie Materieel Organisatie. AVIB 8030-07; Water Displacing Fluid (PX-10/-). 1985

(2) Defensie Materieel Organisatie. AVIB 8030-07/B; Water Displacing Fluid (PX-10/-). 1985

(3) Defensie Materieel Organisatie. C:03/0, PX-10 Water Displacing Fluid. <1985

(4) Defensie Materieel Organisatie. AVIB 8030-07/C; PX-10 Water Displacing Fluid. 1987

White spirit with high aromatic content is mentioned as "carcinogenic" in the Map Book of Chemistry in 2009 (24th edition). This type of white spirit with the CAS No 8052-41-3 was used in early times. The percentage was lowered over time in parallel to the reduction of benzene. More recently produced white spirit has a much lower aromatic content and is therefore sometimes also called "aliphatic white spirit".

The exact composition of PX-10 remains unclear, especially for the time before 1985 and needs to be deduced from the physical properties of the substance: In a document from the UK Ministry of Defence (MOD Def Stan 68-11) PX-10 is described as a water displacing fluid which must consist of protective and surface active materials dissolved in a volatile solvent. This standard defines PX-10 in terms of its properties rather than its composition, including flash point, copper corrosion, weight loss between 46 and 50 hours, water displacing properties, emulsifying properties and stability. The minimum flash point should be 32°C. On the grounds of cost, it seems likely that the solvent will be a boiling point mixture. Some flash points for typical boiling point mixtures are given in Table 2. The minimum flash point of white spirit was defined in BS245:1976 as 32°C. This information is consistent with PX-10 being white spirit or perhaps turpentine-based.

Table 2. Flash points for selected solvent mixtures

Solvent	Flash point (°C)
Petrol	<-40
Naphtha	-30

white spirit (BSI)	32
Turpentine	35
Kerosene jet fuel	60
Diesel fuel	52-96

As the report by the Ministry of Defence indicates white spirit is likely to have contained benzene in the past, as well as toluene and xylene. On page 15 of the report estimates are derived for the possible contents of benzene in PX-10 and how this will have changed over time (Table 3). The estimates are based on the worst case scenario that PX-10 contained 95% of white spirit (see Table 1).

Table 3. Benzene contents of PX-10 as estimated by the Ministry of Defence

Solvent	**Benzene**
Period before 1981	1% [0.2 -2.0%]
Period 1981 to 1985	0.5% [0.2 – 1.0%]
Period 1985 - 1995	<0.1%
After 1995	0%

White spirit is also known as Stoddard Solvent and mineral spirit. Traditional white spirit is produced by fractional distillation of naphtha and kerosene streams of crude oil fractionation. The boiling point range is 130 to 220^{o}C. It contained 25% aromatics, predominantly in the C_7-C_{12} range. There are a number of definitions for white spirit. BSI (1976) defines two types; type A has <25% aromatics and type B has 25-50% aromatic content. The flash point is defined as 32^{o}C.

CEFIC (1989) defines three types of white spirit:

Type 1: Naphtha (petroleum), hydrodesulfurized, heavy
Type 2: Naphtha (petroleum), solvent-refined, heavy
Type 3: Naphtha (petroleum), hydrotreated, heavy.

Types 1 and 2 have boiling ranges from 90-230^{o}C and type 3 has a boiling range of 65-230^{o}C. Straight run white spirit (type 0) has not been treated beyond the process of distillation. Types 1, 2 and 3 white spirit are further divided into 3 grades based on flash points (see Table 4).

Table 4. Flash points for different grades of white spirit

Grade	**Flash point (^{o}C)**	**Boiling point (^{o}C)**
low flash	21-30	130-144
regular flash	31-54	145-174
high flash	>55	175-200

The flash point in PX-10 corresponds to regular flash white spirit.

Traditional white spirit contained less than 0.1% benzene, with some companies now claiming levels in the order of 40ppm (0.004%) and less.

IPCS (1996) quoted publications from the 1970s which reported a benzene content of white spirits of between 0.001 and 0.1%. NIOSH (1977) noted that benzene was typically present in white spirit at around 0.1%. Amoruso et al (2008) reported that the specification for benzene content in mineral spirits is usually <0.1%, but in practice benzene levels are typically below 0.005% (<50 ppm) due to the refining and distillation techniques. CLH (2009) reviewed the composition of white spirit and quoted values from the 1980s and 1990s in the range from <0.001% to 0.1%. Amoruso et al (2008) quote a 1977 study conducted by Battelle Columbus Laboratories on behalf of the U.S. Consumer Product Safety Commission (CPSC) as stating that typical levels of benzene in mineral spirits were in the range of 0.01% to 0.03% (100 to 300 ppm) (quoting Hillman and Simpson, 1978). McKee et al (2007) noted that levels of benzene in mineral spirits have been below approximately 50 ppm since the late 1970s, dropping from 100-200 ppm in 1975. Carpenter et al. (1975) reported that the sample of Stoddard solvent that was used in their toxicological studies contained 0.1% (1000 ppm) benzene and this is widely quoted as evidence of the likely benzene content of white spirit.

As evidence for the carcinogenicity of benzene became accepted, its use became increasing restricted. Since 1976 in Europe, a solvent that contained more than 0.1% benzene had to be classified as a carcinogen.

There appears to be little worthwhile information on benzene in white spirit from before the 1970s. Various papers in the 1950s, 60s and 1970s refer to the use of PX10, white spirit and other solvents (e.g. Elgar, 1973, Ellis, 1957, Stroud and Rhoades, 1953) but none that have been traced so far contain any reference to benzene content of white spirit.

In summary, the benzene content of white spirit would almost certainly have been very much lower than 1% even before the 1970s. The boiling point of regular white spirit is 145-220°C is substantially different from the boiling point of benzene (80°C) and therefore, fractional distillation would have resulted in efficient separation of benzene from the white spirit mixture, whose main aromatic components have 9 or 10 carbon atoms.

Based on our information, a preliminary estimate for the benzene content of white spirit is presented in Table 5. These estimates are

about a 10-fold lower than the estimates given in the Ministry of Defence report.

Table 5. Preliminary estimates of benzene in white spirit

Period	**% Benzene in white spirit**	
	Best estimate	**Upper limit**
before 1970	0.1	0.2
1970-1980	0.03	0.1
1980 onwards	0.01	0.03

Toluene and xylene have higher boiling points than benzene and are present in higher concentrations than benzene. Concentrations of toluene and xylene in white spirit were reported by IPCS (1996) (Table 6).

Table 6. Toluene and xylene content of white spirit (in % volume).

Solvent	% by volume		
	Northern Europe (Varnoline, Henriksen, 1980))	Russia (Henriksen, 1980)	USA (Carpenter et al, 1975)
Toluene	0.005	0.2	0.4
Xylene (o,p & m)	1.1	4.14	1.4*

* C_8 aromatics, includes ethyl benzene.

Clearly the contents of toluene and benzene will vary according to the aromatic content of the white spirit, with low aromatic white spirit having a lower content than traditional white spirit.

Data published by ICPS (1996) indicates that C_9 and C_{10} aromatic hydrocarbons account for over 60% the aromatic content of white spirit. C_{11} and C_{12} aromatics are also likely to be present at concentrations of around 1% and 0.1% by volume.

As previously indicated the most likely alternative to white spirit, based on the minimum flashpoint definition of PX-10, seems to be turpentine. Turpentine is obtained by the distillation of resin from trees, mainly pine trees. It has similar solvent properties as white spirit and is used for thinning oil-based paints, for producing varnishes, and as a raw material for the chemical industry. Its industrial use as a solvent in industrialized nations has largely been replaced by the much cheaper turpentine substitutes distilled from crude oil.

The exact composition of turpentine depends on the species from which it is derived. Broadly, turpentine consists of i) terpenes: 45-75% a-pinene (1), 5-30% b-pinene (2), 2-40% 3-carene (3), ii) other turpentines such as limonene and camphene, and iii) their oxidation products, such as alcohols and aldehydes. Terpenes are a group of hydrocarbons which can be regarded as oligomers of isoprene, 2-methyl-1,3-butadiene (Swedish Chemical Agency 1994). There is no information on benzene being present in turpentine in the literature indicating that benzene in turpentine is unlikely to be a significant hazard.

3. How was PX-10 used over time?

The report described the use of PX-10 by the military. It is possible that PX-10 was already used in the 1950s. It is likely that use was minimal after the 1980s. The report describes several scenarios (high and low exposure scenarios) which were based on documents and interviews with (ex-)military personnel. Without additional focus group meetings it

is not possible to comment on the use-scenarios described. This will need to be addressed in a later stage of the research project.

4. What is known about the possible (additional) health effects that defence personnel might have had due to the use of PX-10?

The main constituents of PX-10 have been identified as i) white spirit (which may include variable amounts of benzene, toluene and xylene), ii) mineral oils possibly containing polycyclic aromatic hydrocarbons; and iii) additives

White spirit
As indicated there is no data available that pertains specifically to the health effects of white spirit. Although it is possible that the different constituents of white spirit could work synergistically or antagonistically there is little data to support this assumption. It seems therefore reasonable to assume that the effects are additive and as such the focus of the health evaluation can be made on the individual constituents.

Benzene
Exposure to benzene can be by inhalation or dermal contact. However, given the high volatility benzene tends to evaporate off the skin more rapidly than it can be absorbed. In non-immersion situations it can be assumed that less than one percent is taken up through the skin (EPA, 2002). This can however change dramatically when hands are immersed in benzene or when occlusion occurs. Therefore, the significance of dermal exposure cannot be determined at this time as information is lacking regarding the exact patterns of dermal exposure.

Health effects related to benzene exposure that are mentioned in the internal report are haematological effects (myeloiddysplastic syndrome, aplastic anaemia, and acute myelogenous leukaemia), immunological and lymphoreticular effects and neurological effects.

It is generally accepted that benzene causes a reduction in the number of circulating erythrocytes, leukocytes and thrombocytes, generally referred to as pancytopenia. Continued exposure can result in aplastic anaemia and leukaemia. As indicated in the report benzene has been causally related to acute non-lymphocytic leukaemia (ANLL; which is primarily comprised of acute myelogenous leukaemia (AML)). However, in a recent re-evaluation of the IARC of benzene, the working group concluded that in addition to ANLL there is also limited evidence that benzene causes acute lymphocytic leukaemia (ALL), chronic

lymphocytic leukaemia (CLL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM) in humans (Baan et al., 2009). A recent meta-analysis of occupational cohort studies published prior to 2009 provided strong evidence for an association between occupational benzene exposure and increased risk of MM, ALL and CLL (Vlaanderen et al., 2010). The association between benzene and NHL is less convincing but this might well be explained by the heterogeneity in the association for particular subgroups of this disease. For instance, two recent case-control studies reported a stronger association with benzene with follicular lymphoma (FL) than for diffuse large B-cell lymphoma (DLBCL) (Cocco et al., 2010; Wong et al., 2009). This together with the substantial experimental and molecular epidemiological evidence that benzene exposure alters key components of the immune system relevant for lymphomagenesis (e.g. CD4+ T cell level; CD4+Tcell/CD8+ T cell ratio) (Lan et al., 2004), provide support that benzene is likely to be causally related to one or more subtypes of lymphoma.

As mentioned in the report there is indeed evidence that more recent exposure to benzene is more important for AML. This observation however cannot be extended necessarily to lymphomas given the different pathogenesis and the lack of epidemiological data supporting or refuting this notion.

Limited studies suggest that benzene may cause effects on the peripheral nerves and/or spinal cord. Symptoms included an increased incidence of headaches, fatigue, difficulty sleeping and memory loss among workers with significant exposures (EPA, 2002).

Furthermore, prolonged or repeated contact with benzene can cause redness, dryness, cracking (dermatitis) due to the defatting action of benzene.

Toluene

The health effects associated with toluene exposure mentioned in the report are neurological effects (most seriously chronic encephalopathy). Numerous studies of rotogravure printers, painters and rubberized-matting workers with long-term exposure to toluene are inconclusive about the potential of toluene to cause central nervous system (CNS) damage (Baslo and Aksoy, 1982; Snyder, 2000; Filley et al., 2004). Most studies do not have good exposure data, several indicate alcohol consumption as a confounder and few have used the neurobehavioural tests recommended by the World Health Organization. Some studies reported changes such as memory loss, sleep disturbances, loss of ability to concentrate, or incoordination, while others report no effects. Recent studies using sensitive neurobehavioural tests have shown altered scores for exposed workers but whether or not these results actually indicate CNS damage is not clear. Other studies have shown no change in neurobehavioural performance for workers with long-term exposure to toluene.

A review of several studies on toluene and its effects on colour vision concluded that the evidence is inconclusive as to whether long-term exposure to toluene results in a persistent impairment of colour vision (ATSDR, 2000). Similarly, the evidence of hearing loss due to toluene exposure is limited. Hearing loss has been observed in workers in some studies following long-term exposure to toluene and noise and in animals exposed to very high concentrations of toluene.
Several occupational studies have reported on the reproductive outcomes among women exposed to toluene. Studies on spontaneous abortion provided the most convincing evidence for an association with toluene. However, the potential for bias and multiple chemical exposures suggests that the results from these studies should be interpreted cautiously (Health Council, 2008). Few data are available regarding the effects of toluene on human male reproduction. In the report of the Dutch Health council it was concluded that the available data give weak indications for an association between paternal exposure to toluene and spontaneous abortion (Health Council, 2008).
In the EU toluene is classified as toxic to reproduction Category 3 (substances which cause concern for humans owing to possible developmental toxic effects). This requires use of the risk phrase R63, (possible risk of harm to the unborn child) (RAIS, 1994).
Repeated or prolonged contact with toluene may cause dermatitis (red, itchy, dry skin) because of its defatting action.

Xylene
The health effects associated with xylene exposure mentioned in the report are neurological effects (chronic encephalopathy). Indeed long-term xylene exposure may cause harmful effects on the nervous system, but there is not enough information available to draw firm conclusions. Symptoms such as headaches, irritability, depression, insomnia, agitation, extreme tiredness, tremors, and impaired concentration and short-term memory have been reported following long-term occupational exposure to xylene and other solvents (ATSDR, 2007). Unfortunately, there is very little information available which isolates xylene from other solvent exposures in the examination of these effects.

Xylene has been linked to reproductive effects in some but not all studies. The Health Council concluded in their report that the available data indicate a weak association between maternal exposure to xylene and spontaneous abortion (Health Council, 2009).

Besides possible neurological effects chronic health effects after prolonged exposure to xylene are dermatitis (dryness and cracking).

Mineral oils
Untreated and mildly treated mineral oils are known to be human carcinogens based on sufficient evidence of carcinogenicity in humans

that indicates that exposure to these types of mineral oils causes cancer. The carcinogenicity of exposure to mineral oils has been evaluated in numerous studies in a variety of occupations including metal working, jute processing, mule spinning, newspaper press operation, and other newspaper work (NTP, 2009). Exposure to mineral oils was consistently and strongly associated with an increased risk of squamous cell cancers of the scrotum and skin.

Mineral oils are a complex mixture of different oils that can contain PAHs. It is likely that the described health effects such as skin cancer can be ascribed to the PAHs present in mineral oils. Besides skin cancer PAHs have been linked to lung and bladder cancer (Baan et al., 2009). It is unclear why the latter two are not mentioned in the report. However, these cancers have been observed in populations with high occupational exposures to PAHs. Given the low content of mineral oils in PX-10 and the low contents of PAHs in mineral oils it can be expected that PAH exposures would have been low. Given the low volatility of mineral oils the most important exposure route will have been dermal.

Additives or other compounds

Besides the aforementioned major constituents PX10 contained fatty esters (0.5 – 1.5%) and unknown additives (max 6%). As it is unknown which fatty esters were used it is difficult to assess the potential health effects. However, health effects associated with fatty acids are generally minimal with the exception potentially for glycol ether fatty acid esters which have been associated with reproductive effects. Other compounds or additives are not specified and as such no meaningful health risk assessment can be performed.

In summary the described health effects in the report seems reasonably accurate with the exception of the cancer sites related to benzene exposure and the possible reproductive effects associated with solvent exposure.

5. Which questions need to be answered by scientific organisations in order to answer open questions?

The report identifies two main questions. The first is related to the use and possible exposures associated with the use of PX-10. The second question is related to the estimation of the risk of developing a serious health complaint due to the use of PX-10.

Although, there is uncertainty around the composition of PX-10 exposure can be reconstructed assuming likely concentration ranges of the different constituents. Together with more detailed information on the likely use scenarios exposure distributions can be estimated using for instance probabilistic mass balance models. Given the nature of the

exposure these models will need to incorporate both dermal and inhalation exposure.

The health risk of most concern related to use of PX-10 are mostly related to potential benzene exposure and hemato- and lymphopoetic cancers. Although, solvent exposures have been linked to neurological effects the scientific literature is not consistent. This is certainly true regarding the specific constituents and the dose-response relationships. As such it seems that the risk estimation should focus on benzene exposure and hemato- and lymphopoetic cancers. However, if the nature of the current claims is such that other health endpoints should be considered this can be explored further but would probably not lead to a quantitative assessment of risk associated with the use of PX-10.

6. Summary conclusion

The internal report of the Ministry of Defence regarding the composition, use and associated health effects of PX-10 seems largely consistent with the current scientific literature. However, we note that the estimation of the benzene contents of PX-10 might have been too high. In addition, we noted several additional possible health effects associated with the different constituents of PX-10.

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