Regulatory Toxicology and Pharmacology 70 (2014) 222–230

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

The sub-chronic toxicity of regular White Spirit in rats

Juan-Carlos Carrillo [a,*], M. David Adenuga [b], Richard H. Mckee [b]

[a] Shell Health, Shell International B.V., P.O. Box 162, 2501 AN The Hague, The Netherlands
[b] ExxonMobil Biomedical Sciences, Inc., 1545 Route 22 E., Annandale, NJ 08801, USA

ARTICLE INFO

Article history:
Received 26 May 2014
Available online 9 July 2014

Keywords:
Alkanes
Aromatic hydrocarbons
Sub-chronic toxicity
Inhalation toxicity
Occupational exposure limit
Liver enlargement
UVCB
Hydrocarbon solvent
Stoddard solvent
White spirit

ABSTRACT

Hydrocarbon solvents are mostly complex substances (UVCB) with carbon numbers in the range of approximately C5–C20. One of the most common types is a C9–C14 aliphatic solvent containing approximately 20% aromatics and commonly known as White Spirit in Europe and mineral spirits in the US. In previous repeated inhalation toxicity studies, White Spirit was reported to cause minimal systemic effects in most animal species with few effects other than male rat-specific kidney changes at levels up to approximately 2000 mg/m^3. In the present study male and female rats were exposed to White Spirit vapors, 6 h/day, 5 days/week for 13 weeks at levels of approximately 2000, 4000, or 8000 mg/m^3 to assess the potential for effects at higher exposure levels. All of the rats survived the treatment period. In life observations were largely restricted to acute central nervous system (CNS) effects in the high exposure group. Terminal body weights of high exposure groups animals were significantly below control values. Statistically significant differences in the clinical and hematological observations were small and within normal physiological limits. Weights of some organs including liver, spleen and kidneys were elevated, but microscopic examination indicated that the only pathological effects were changes in the kidneys of the male rats, consistent with an α2u-globulin-mediated process, which is gender and species-specific and not relevant to humans. The overall no observed adverse effect level (NOAEC) was 4000 mg/m^3.

1. Introduction

The hydrocarbon solvents discussed in this paper are members of a group of complex substances described by the industry as C9–C14 aliphatic solvents with aromatic constituents at levels between 2% and 25% and boiling in the range of approximately 140–220 °C. The prototypic substance of this type is "Stoddard solvent", a desulfurized solvent fractionated from crude oil by distillation, with a boiling range of 149–204 °C, and containing approximately 15–25% aromatic compounds (primarily trimethylbenzene and ethyltoluene isomers), depending on the characteristics of the crude oil from which it was produced. Solvents of this type are commonly referred to in the United States as Type 1 mineral spirits and in Europe as "White Spirit", although "Stoddard solvent" is still used in the dry cleaning industry (see for example ASTM D-235). With the advent of the United States Environmental Protection Agency's (USEPA) Toxic Substances Control Act (TSCA), this substance was entered into the TSCA inventory under Chemical Abstract Services (CAS) Registration Number 8052-41-3. In order to distinguish hydrocarbon solvents from the petroleum refining streams from which they are derived, the hydrocarbon solvents industry developed a nomenclature (i.e., the naming convention) which more precisely defines the solvents in terms of constituent types and carbon number ranges. The naming convention was used in Europe for REACH (Registration, Evaluation, Authorization and Restriction of Chemicals, EU, 2006) registrations, and also as a means of describing these solvents to satisfy high production volume (HPV) commitments (OECD, 2012). Under this convention, "White Spirit" is actually a reference to a group of hydrocarbon solvents with aromatic constituents generically described as, *Category 3: C9–C14 Aliphatics (2–25% Aromatics)*. Members of this category may include solvents with narrower carbon ranges (e.g. C9–C12) and varying aromatic content between 2% and 25%.

Data presented in Table 1, indicates that, although there are small compositional differences, the overall composition of White Spirit solvent has remained relatively constant over the past 40 years despite differences in sample origin and time of production. Some compositional variation is expected because depending on the type of crude oils used, the final White Spirit solvent will fluctuate in both alkane and aromatic content and constituents.

* Corresponding author.
E-mail address: juan-carlos.carrillo@shell.com (J.-C. Carrillo).

http://dx.doi.org/10.1016/j.yrtph.2014.07.007
0273-2300/

Table 1
Approximate hydrocarbon composition of White Spirit over the past 40 years in terms of carbon number and hydrocarbon constituents: normal and n- and iso-paraffins, (naphthenics iso-alkanes, cyclo-alkanes) and aromatics.

Hydrocarbon constituents by carbon number	Pre 1980		Post 1980		
	Kuwait sample	Arabian light sample	EU sample 1982	EU sample 1985	EU sample 2011
Paraffins (*n* + *iso*)	Approximate constituent concentrations in % w/w				
C8	⩽0.5	⩽0.5	⩽0.5	⩽0.5	–
C9	13	13	10	12	7
C10	33	33	24	24	20
C11	13	12	16	15	17
C12	2	2	3	3	3
C13	–	–	–	–	⩽0.1
Sum *P*	61	60	53	54	47
Naphthenes					
C8	⩽0.5	⩽0.5	⩽0.5	⩽0.5	⩽0.1
C9	5	5	7	8	8
C10	8	8	11	10	14
C11	4	4	8	7	10
C12	1	1	2	2	2
Sum *N*	18	18	28	27	34
Aromatics[*]					
C8	1	1	1	2	⩽1
C9	11	11	9	9	8
C10	6	6	7	6	6
C11	2	2	3	2	3
C12	–	–	–	–	⩽1
Sum *A*	20	20	20	19	18
Carbon number range					
C7	⩽0.1	⩽0.1	–	–	–
C8	2	2	2	3	⩽0.1
C9	29	30	26	29	23
C10	48	48	41	40	40
C11	18	18	26	23	31
C12	3	3	5	4	5
C13	⩽1	⩽1	⩽1	⩽1	⩽0.1

[*] Predominantly branched mono-aromatics.

This fluctuation however does not imply that there will be large differences in overall composition such as new (non-hydrocarbon) constituents entering or existing constituents totally disappearing from the final product. These constituents in the C9–C14 range include aliphatic constituents – normal, iso-paraffins and naphthenics (n, iso and cyclo-alkanes respectively) whereas the aromatic fraction constituents are predominantly branched mono-aromatics. Naphthalene may be present, but at levels below classification limits.

As can be seen from the compositional data, over time a gradual shift towards higher molecular weight components (e.g. decrease in C9 to an increase in C11) and a move from n-and iso-alkanes towards cyclo-alkanes can be observed. The concentration and make up of aromatics has basically remained constant.

Despite this variation in individual hydrocarbon constituents the technical properties and toxicological effects have not substantially changed.

In regards to toxicity, effects after repeated exposure to solvents of this type were first investigated by Rector et al. (1966) in sub-chronic inhalation studies in a number of animal species including rats, guinea pigs, rabbits, dogs and monkeys. The animals were exposed continuously (i.e., 24 h/day) for 90 days at graded concentrations ranging from 114 to 1271 mg/m^3. Aside from the guinea pigs, the majority of the animals survived, and, at termination, had body weights similar to control values. The gross pathological investigation revealed lung congestion in high exposure group animals of all species. There were histologic changes in livers of some animals and some small hematologic changes, but the authors did not consider these to have been exposure related. The no effect level for all species other than guinea pigs was reported as 1271 mg/m^3. The guinea pigs were much more profoundly affected than animals of other species with mortalities at concentrations as low as 363 mg/m^3 and a no effect level of 238 mg/m^3.

Due to the striking species differences in response, additional studies were conducted in which animals were exposed repeatedly 8 h/day, 5 days/week for 10 weeks at exposure levels ranging from 593 to 1353 mg/m^3 (Rector et al., 1966). In this study all of the animals including the guinea pigs survived to scheduled termination. There was some evidence of lung irritation, but there were no histological changes in animals other than guinea pigs.

A later experiment (Jenkins et al., 1971) assessed whether the toxicity in guinea pigs had been exacerbated by insufficient dietary levels of vitamin C. It was shown that when guinea pigs were maintained on a diet with high levels of ascorbic acid, they were much less sensitive to the effects of White Spirit solvent, suggesting that the unusual sensitivity of the guinea pigs was due more to dietary issues than to exposure to White Spirit.

In 1975 Carpenter et al. (1975) reported a study in which Wistar rats and beagle dogs were exposed to Stoddard solvent 6 h/day, 5 days/week for 13 weeks. Exposure levels were approximately 500, 1100, or 1900 mg/m^3. All animals survived without outward signs of distress. There were no remarkable findings in the clinical or hematological evaluations. There were no pathological findings in the dogs, but marked tubular regeneration was noted in kidneys of male rats exposed at the 1100 and 1900 mg/m^3 levels. Later studies showed that the kidney lesions were the consequence of an α-2u globulin-mediated process and not relevant to humans (NTP, 2004). Aside from the male rat kidney effects, Carpenter et al. (1975) reported the overall no effect level in this study for both rats and dogs to be 1900 mg/m^3.

Based on a review of the toxicological literature, Amoruso et al. (2008) concluded that White Spirit was not toxic when