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Local and systemic toxicity of JP-8 from cutaneous exposures

James N. McDougal [a,*], James V. Rogers [b]

[a] *Department of Pharmacology and Toxicology, Wright State University School of Medicine, 3640 Col Glenn Highway, Dayton, OH 45435, USA*
[b] *Battelle Memorial Institute, Medical Research and Evaluation Facility, 505 King Avenue, Columbus, OH 43201, USA*

Abstract

Jet propellant-8 (JP-8) jet fuel is a version of commercial jet fuel, Jet A, and is a complex mixture of primarily aliphatic (but also aromatic) hydrocarbons that varies in composition from batch to batch. There is potential for dermal exposure to jet fuels with personnel involved in aircraft refueling and maintenance operations as well as ground personnel. Cutaneous exposures have the potential to cause skin irritation, sensitization or skin cancer. JP-8 has been shown to be irritating and causes molecular changes in the skin of laboratory animals. The mechanisms of some of these effects have been investigated in intact skin and cultured skin cells. Hydrocarbons have also been shown to cause skin cancer with repeated application to the skin. Additionally, there is concern about systemic toxicity from dermal exposures to jet fuels, such as JP-8. Assessing risks from systemic absorption of hydrocarbon components is complex because most of the components are present in the mixture in small quantities (less than 1%). The effect of the fuel as a vehicle, different rates of penetration through the skin and different target organ toxicities all complicate the assessment of the hazards of cutaneous exposures. The purpose of this manuscript is to review studies of local and systemic toxicity of JP-8.

Keywords: JP-8 jet fuel; Skin irritation; Skin sensitization; Systemic toxicity

1. Introduction

Jet propellant-8 (JP-8) is an aviation fuel that is related to kerosene and has additives to improve performance. This hydrocarbon fuel is the primary fuel used by the US and North Atlantic Treaty Organization militaries and is related to commercial aviation fuels (Jet A and Jet A-1). The transition from the previous jet fuel (JP-4) was a 20 year process started in the 1980s designed to improve safety and improve distribution problems (Zeiger and Smith, 1998). JP-8 has a higher flash point than JP-4 and is less likely to ignite accidentally. JP-8 is a multipurpose fuel that is also used in ground vehicles, generators, heaters and stoves (Makris, 1994). Now, estimates of worldwide use are approximately five billion gallons (approximately 19×10^9 l) per year (Henz, 1998; Zeiger and Smith, 1998). Because of the volumes produced and the multipurpose nature of the fuel, there is potential for exposures to JP-8 in several forms—aerosol, vapor or liquid.

Occupational exposures to jet fuel may occur during fuel transport, aircraft fueling and defueling, aircraft maintenance, cold aircraft engine starts,

* Corresponding author. Tel.: +1-937-775-3697; fax: +1-937-775-7221.
E-mail address: james.mcdougal@wright.edu (J.N. McDougal).

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maintenance of equipment and machinery, use of tent heaters, and cleaning or degreasing with fuel (Centers for Disease Control (CDC), 1999; Subcommittee on Jet-Propulsion 8 fuel of Committee on Toxicology, 2003). Skin can be an important route of exposure because of the potential for liquid and aerosol contact with fuel. Skin contact with JP-8 vapors would not be expected to be a concern because of research with whole-body vapor penetration of volatile organic chemicals in rodents (McDougal et al., 1985) and humans (Corley et al., 1997; Riihimaki and Pfaffli, 1978). This work suggests that, unless an individual was wearing a respirator, inhalation of vapors would overwhelm the small amount of vapor that would penetrate through the skin. Liquid contact with jet fuels would come primarily from spills, splashes or handling parts wet with fuel. Aircraft fuel maintenance workers may be exposed to liquid fuel for more than 10 min (Subcommittee on Jet-Propulsion 8 fuel of Committee on Toxicology, 2003). In cold climates, JP-8 aerosol may be formed when a cold jet engine is started because JP-8 has a low flash point (Subcommittee on Jet-Propulsion 8 fuel of Committee on Toxicology, 2003). This plume coming from the jet engine for a short period of time on startup is visible as a white cloud and contains fuel aerosol droplets in addition to ice crystals. A crew chief standing in this plume might get enough JP-8 aerosol on the clothing and skin to cause concern about skin penetration. Interestingly, the composition of liquid and aerosol JP-8 may vary with time and be different from each other due to loss of the volatile components.

JP-8 is a complex mixture that may contain aliphatic and aromatic hydrocarbons ranging from about 9 to 17 hydrocarbons, including thousands of isomers and three to six performance additives (Subcommittee on Jet-Propulsion 8 fuel of Committee on Toxicology, 2003). JP-8 is a performance-based fuel and therefore the composition can vary from batch to batch. Performance specifications are set for boiling point (500 °F, 260 °C), maximum amount of sulfur (0.3%), maximum olefins (5%) and maximum aromatic content (22%). On average the composition is: 33–61% *n*-alkanes and isoalkanes, 10–45% naphtenes, 12–22% aromatics, and 0.5–5% olefins (Vere, 2003). Because of the variability in composition, researchers funded by or associated with the US Air Force use fuel from a common source, a partial analysis of which is shown in Table 1. JP-8 also may contain additives as shown in Table 2. The ice inhibiting additive added in the largest proportion (diethylene glycol monomethyl ether, DIEGME) is still a very small component at 0.1% of the fuel mixture.

Table 1
Composition of a JP-8 sample analyzed by graph chromatography (McDougal et al., 2000)

Component	Percentage (w/w)
Undecane	6.0
Dodecane	4.5
Decane	3.8
Tridecane	2.7
Tetradecane	1.8
Methyl naphthalene	1.2
Nonane	1.1
Trimethyl benzene	1.0
Pentadecane	1.0
Dimethyl naphthalene	0.78
Dimethyl benzene (xylene)	0.59
Naphthalene	0.26
Ethyl benzene	0.15
Diethylene glycolmonomethyl ether	0.08
Methyl benzene	0.06

Because JP-8 is a complex mixture, assessing hazard and risk is not an easy task. Not only may fuel at different locations in the world be different due to batch to batch variability, but fuel that is exposed to the air for any length of time will have a loss of the more volatile components. Also JP-8 vapor will have a different composition from liquid and JP-8 aerosols will be somewhere in-between depending on the age of the aerosol.

In general, the toxicity of petroleum hydrocarbons (specifically kerosene) has been fairly well-studied (Agency for Toxic Substances and Disease Registry (ATSDR), 1998; Nessel, 1999; Ritchie et al., 2003; Subcommittee on Jet-Propulsion 8 fuel of Committee on Toxicology, 2003). The neurotoxicity of JP-8 is not well established; however, animal studies have investigated the neurobehavioral effects of several jet fuels following inhalation exposure and found differences from control (Baldwin et al., 2001; Ritchie et al., 2001; Rossi et al., 2001). Human epidemiological studies report that individuals exposed to jet fuel sometimes report acute symptoms on exposure and do poorly on neurobehavioral tests (Knave et al., 1978, 1979). Preliminary results from a U.S. Air Force epidemiological

Table 2
Additives used in JP-8 (adapted from Baker et al., 1999a)

Additive	Function	Quantity	Required or optional
DIEGME[a]	Ice inhibitor	1 ml/l	Required
Stadis 450[b]	Static inhibitor	2 mg /l	Required
DCI-4A[b]	Corrosion inhibitor	15 mg/l	Required
Antioxidant[c]	Inhibits gum formation	25 ppm	Optional
Metal deactivator[d]	Controls metal catalyzed fuel deterioration	3 ppm	Optional

[a] Diethylene glycol monomethyl ether.
[b] Proprietary formulation.
[c] *N,N*-Diisopropylparaphenylene diamine or various blends of hindered phenols.
[d] *N,N*-Disalicylidene-1,2-propanediamine or *N,N*-disalicylidene-1,2-cyclohexanediamine.

study, as reported by the Committee on Toxicology of the NAS (Subcommittee on Jet-Propulsion 8 fuel of Committee on Toxicology, 2003), suggest there may be central nervous system effects with JP-8 exposures. JP-8 oral exposure does not profoundly alter many immunological endpoints, but does decrease delayed type hypersensitivity and suppress antibody-specific IgM immune responses (Peden-Adam et al., 2001). Genetic toxicity has been reported for kerosene and Jet A (Koschier, 1999) in some of the standard in vitro tests. Related middle distillates are not mutagenic in the assays for mutagenicity unless they contain high levels of polycyclic aromatic hydrocarbons (McKee et al., 1994). Few reproductive/developmental studies are available. One study of sperm quality in men exposed to jet fuel found no changes (LeMasters et al., 1999). Reproductive studies (male and female) in laboratory animals are generally negative (Mattie et al., 1995; Schreiner et al., 1997; Subcommittee on Jet-Propulsion 8 fuel of Committee on Toxicology, 2003). JP-8 and related jet fuels would be classified as relatively harmless orally (Neely, 1994) based on the acute oral LD_{50} of much more than 5 g/kg (Agency for Toxic Substances and Disease Registry (ATSDR), 1998). There is no inhalation LD_{50} established for JP-8 or kerosene (Agency for Toxic Substances and Disease Registry (ATSDR), 1998). The purpose of this paper is to review the local and systemic toxicity of JP-8 from cutaneous exposures.

2. Local toxicity

Toxicity to the skin as a direct result of chemical contact can fall into several categories. Chemicals can irritate the skin, cause an immune response or result in the unregulated cell growth which we call cancer. In many cases we do not know the mechanisms, but we can observe the symptoms that result from the chemical interactions. JP-8 and other kerosene-based fuels have been shown to cause skin irritation, skin sensitization and skin tumors with repeated or prolonged contact.

2.1. Irritation

Skin irritation is a non-immune-related response characterized by direct action of a compound on skin tissues (Weltfriend et al., 1996). Irritant dermatitis can be caused by a wide variety of compounds such as surfactants, solvents, oils, hydrocarbons (Wahlberg, 1993; Wigger-Alberti et al., 2000), but the underlying mechanisms are not completely known.

Methods to measure irritation include measurements of skin condition, release of inflammatory cytokines and in vitro studies of the primary epidermal cell, the keratinocyte. JP-8 exposure to the skin causes erythema and edema, as indicated visually and by changes in histology at periods of 1 h to 4 weeks in hairless rats, rats and pigs (Baker et al., 1999a,b; Kabbur et al., 2001; Kanikkannan et al., 2001b, 2002; Monteiro-Riviere et al., 2001). Transepidermal water loss, which is often used as a measure of skin condition, increases with JP-8 exposure (Kanikkannan et al., 2001b, 2002; Monteiro-Riviere et al., 2001). Kabbur et al. (2001) showed that a 1 h, cutaneous, JP-8 exposure to rats caused increases in inducible nitric oxide synthase and interleukin-1 protein. Increased levels of oxidative species and low molecular weight DNA are also present after brief exposures to JP-8 (Rogers et al., 2001).

Cultured skin cells are often used to assess irritation of chemicals to the skin. In vitro assessment of the cytotoxic and/or irritating potential of volatile organic chemicals (VOCs) is problematic due to their physical properties. VOCs are practically insoluble in water and can evaporate rapidly from the exposure medium over time leading to a non-uniform or unknown chemical dose throughout the exposure period, which may ultimately affect the interpretation of dose-response relationships. Exposure of cultured cells to jet fuel (including JP-8 and JP-8 components) has led to the measurement of observed biological effects including cytotoxicity, cytokine release, DNA damage, and oxidative stress, indicating the toxic and pro-inflammatory ability of JP-8 and JP-8 components (Boulares et al., 2002; Chou et al., 2002, 2003; Jackman et al., 2002; Wang et al., 2002). The components of JP-8 possess varying degrees of water solubility and volatility, which can make it difficult to relate the experimental exposure dose with the dose added to the cells (Rogers and McDougal, 2002; Coleman et al., 2003). Therefore, an important step towards utilizing in vitro assessment of JP-8 irritation potential would be to relate the chemical dose at the target tissue/cellular site that is promoting biological-responses.

Recently, Chou et al. (2003) demonstrated differences in the cytotoxicity and IL-8 release in human epidermal keratinocytes (HEK) exposed to JP-8 components while cultured in unsealed plates. It appears that in HEK cells, the aromatic hydrocarbons cause greater direct cytotoxicity than aliphatic hydrocarbons, while the aliphatic compounds induce a higher pro-inflammatory response as measured by IL-8 release. In murine keratinocytes exposed in an unsealed culture system, we have also seen a similar trend in which aromatic JP-8 components (*m*-xylene and 1-methyl naphthalene) appear more cytotoxic than the aliphatic *n*-nonane when comparing EC_{50} values (Rogers et al., 2004). However, in murine keratinocytes exposed in sealed containers where the chemical concentration is stable throughout exposure, this relationship of the cytotoxic potency (based on EC_{50} values) of aromatic and aliphatic hydrocarbons is different. It appears that *m*-xylene is the most potent, followed by *n*-nonane, and 1-methyl naphthalene as the least potent. This difference could be attributed to chemical partitioning, which seems to play an important role in the cytotoxicity of VOCs (Rogers et al., 2004).

In conclusion, there is no doubt that JP-8, like most of the kerosene-based fuels, causes skin irritation with prolonged or repeated contact to the skin. Ultimately, in vivo and in vitro data could be used for the development of a biologically-based mathematical model that could be used to predict the dose and duration of exposure that would result in JP-8 induced skin irritation. A crucial step in the development of a predictive model is to be able to calculate the chemical concentration at the target site (e.g., epidermis) that promotes the onset of dermal irritation. Understanding the irritant mechanism of action may help design prophylactic or therapeutic intervention to jet fuel exposures.

2.2. Sensitization

Allergic dermatitis is a delayed (type IV) hypersensitivity reaction that involves cell-mediated immune responses (Marzulli and Maibach, 1996). JP-8 is classified as a weak skin sensitizer (Kinkead et al., 1992) based on studies where guinea pigs were cutaneously treated with 0.1 ml JP-8 four times in a 10-day period before the challenge. Three jet fuels tested (JP-8, JP-8 plus 100 and Jet A) were active in the murine local lymph node assay indicating that they are weak sensitizers (Kanikkannan et al., 2000). JP-8 affects the sensitization to other antigens, because after single or repeated JP-8 treatments to the ears of mice, the induction of contact hypersensitivity to dinitrofluorobenzene (Ullrich, 1999) and *Candida albicans* (Ramos et al., 2002) was impaired in a dose-dependent manner. Similar studies (Ullrich, 1999; Ullrich and Lyons, 2000) found that T-cells isolated from JP-8 treated mice had reduced proliferation in vitro, but that antibody production was identical in treated mice compared to controls. The proposed mechanism of interference with an immune response was though the release of immune biological-response modifiers such as prostaglandin E_2 and interleukin-10 (Ullrich and Lyons, 2000). Much more research needs to be done to understand if the immunological changes seen with cutaneous dosing of JP-8 in laboratory animals would relate to any human health consequences other than skin sensitization.

2.3. Skin tumors

Two year carcinogenicity studies (skin painting) in mice with Jet A produced marked skin irritation and skin tumors in 44% of the mice (Freeman et al., 1993). In similar studies using an intermittent schedule to reduce skin irritation, the number of tumors was reduced to 2%. Freeman et al. (1993) suggests that irritation is necessary but not sufficient for tumor formation. Jet A applied to the skin of mice three times a week for 105 weeks caused squamous cell carcinoma and fibrosarcoma tumors (Clark et al., 1988). Hydrotreated fuel (which has less sulfur) was less tumorigenic (Clark et al., 1988; Freeman et al., 1990, 1993). Skin tumors caused by occupational exposures to JP-8 are unlikely for two reasons. First, the chronic repeated application of jet fuel to the skin required to cause severe irritation and tumors in rodent studies is not a realistic scenario for human exposures because workers would limit exposures to avoid the irritation. Second, the specification that limits the sulfur content to less than 0.3% would reduce the tumorigenicity of JP-8 if prolonged exposure occurred.

3. Systemic toxicity

Systemic toxicity from cutaneous exposures to JP-8 would be expected to be similar to toxicity from inhalation or ingestion. Once the chemical enters the body, it is the concentration at the target organ that causes the toxicity. The exposure route will influence the dosimetry to the target organ, but the ultimate systemic toxicity will depend on target tissue levels of JP-8 components. Local toxicity at the exposure site will be dependent on the exposure route. Chronic exposure to JP-8 by inhalation might be expected to result in pulmonary inflammation just as prolonged dermal exposures might result in skin irritation. There are very few toxicity studies with JP-8 applied dermally. One 40 week study in male and female Balb/c mice where the animals were dosed three times a week (41.5 mg/kg per day) only resulted in changed organ and body weights (Schultz et al., 1981). Thirty grams per kilogram per day of another kerosene-based fuel (JP-5) dermally dosed seven times a week for 2 weeks in female mice resulted in 100% mortality (NTP/NIH, 1986). Dermal studies for 13 weeks with hydrodesulfurized kerosene showed that 494 mg/kg did not induce reproductive, developmental or neurotoxicity effects (Koschier, 1999). These studies suggest that, like oral and inhalation toxicity, JP-8 would not be very toxic with the dermal route. One problem with dermal exposure studies is that it is often very hard to have a “pure” dermal exposure. During dermal studies it is possible for animals to get an oral dose through grooming or an inhalation dose of volatile chemical from evaporation from the skin. One way to try to estimate systemic toxicity is to measure the penetration of a chemical through the skin and estimate the body burden based on an anticipated exposure scenario (McDougal and Boeniger, 2002).

3.1. In vitro penetration studies

In vitro skin penetration studies are accomplished by placing excised pieces of animal or human skin between a donor chamber and a receptor chamber and evaluating the appearance of chemical in the receptor chamber over time. There are too many variations in methods including vehicles, skin preparation and receptor solutions and type of diffusion cell (flow-through or static) to address here, see Franz (1978), Bronaugh (1995), or Bronaugh and Stewart (1985). Another variation is the way penetration through the skin is expressed—flux, permeability or percent absorbed, see Poet and McDougal (2002) for advantages and disadvantages of each. The fact that JP-8 is a complex mixture, causes difficulties with studies designed to measure penetration of JP-8 and its components through the skin. Because no individual hydrocarbon components of JP-8 make up more than 6% of the mixture (Table 1) and only nine are present at 1% or more, it is hard to have the analytical detection limit to measure penetration of components through the skin. There are two approaches in the literature for measurement of penetration of JP-8 components. The first and more popular approach is to add one or more radioactive constituent hydrocarbons as markers to JP-8 and detect the penetration of radioactivity through the skin (Baynes et al., 2001; Kanikkannan et al., 2001a,b; Riviere et al., 1999). These studies generally show that the aromatics (toluene and naphthalene) penetrate the skin better than the aliphatics (decane, dodecane, tridecane and

Table 3
Fluxes (±S.D.) and permeability coefficients for JP-8 components from 4 h diffusion cell experiments with rat skin (adapted from McDougal et al., 2000)

Component	Flux (μg/cm^2 h)	Permeability coefficient (cm/h)
Methyl benzene (toluene)	0.54 ± 0.09	1.1×10^{-3}
Naphthalene	1.04 ± 0.38	5.1×10^{-4}
Ethyl benzene	0.38 ± 0.15	3.1×10^{-4}
Dimethyl benzene (xylene)	0.80 ± 0.24	1.7×10^{-4}
Methyl naphthalene	1.55 ± 0.52	$l.6 \times 10^{-4}$
Trimethyl benzene	1.25 ± 0.50	1.3×10^{-3}
Dimethyl naphthalene	0.59 ± 0.17	9.3×10^{-5}
Decane	1.65 ± 0.68	5.5×10^{-5}
Nonane	0.38 ± 0.24	4.2×10^{-5}
Undecane	1.22 ± 0.81	2.5×10^{-5}
Tridecane	0.33 ± 0.19	1.5×10^{-5}
Dodecane	0.51 ± 0.36	1.4×10^{-5}

hexadecane). The flux of each component is proportional to concentration of the component in JP-8 (Kanikkannan et al., 2001b; McDougal et al., 2000). Another way is to apply JP-8 and to measure the penetration of individual hydrocarbons that penetrate the skin in sufficient quantities to be detectible. Table 3 shows 13 components of JP-8 penetrated rat skin in diffusion cells well enough to be detected individually, and summarizes the fluxes (defined as the mass penetrating per surface area exposed and time of exposure) and permeability coefficients (defined as the theoretically concentration-independent measure of penetration expressed as distance per time) for these compounds (McDougal et al., 2000).

Permeability measurements generally show that the permeability is related to molecular weight (chain length) and lipophilicity (octanol–water partition coefficient) (McDougal and Boeniger, 2002). Once measurements of JP-8 component concentration are done they can be used to estimate the amount of each component that would be absorbed from a JP-8 exposure based on exposure area and time.

3.2. Estimates of systemic toxicity calculated from in vitro experiments

The total amount of JP-8 absorption has been estimated for realistic exposure scenarios. Based on a steady-state JP-8 flux of 20.3 ug/cm^2 h from rat skin studies (McDougal et al., 2000) about 17 μg would penetrate the skin of both hands in an hour. Using oral reference doses (mg/kg per day) for hydrocarbon components (aromatic and aliphatic) adjusted for differential flux, a route to route extrapolation suggests that a 70 kg person could absorb 6.37 mg per day, 7 days a week for a lifetime without appreciable risk. This would equate to about 22 min per day exposure to both hands (McDougal et al., 2000) and suggests that exposure to JP-8 in most scenarios would not cause systemic toxicity.

4. Conclusions

JP-8 has potential for dermal exposures to aerosol, liquid and vapor due to widespread use in the military. JP-8 is a complex and variable mixture that is related to other kerosene-based fuels that show several different toxicities in laboratory animal studies. The local toxicity of JP-8 on the skin is recognized due to animal studies that show skin irritation, sensitization and cancer with prolonged exposures. Systemic toxicity from dermal exposures to JP-8 may occur with prolonged or repeated exposures. More research is needed to be able to perform appropriate risk assessments for the dermal route.

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