

## Invited Editorial

### The Significance of Skin Exposure

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When science is confronted by complex tasks and simpler ones, it is often the simpler tasks that get done first. One only has to look at the currently large number of air contaminant exposure limit criteria and compare that to the virtual absence of quantifiable skin exposure guidance to appreciate this statement.

Early occupational health professionals did recognize that many workers were being poisoned as a consequence of getting chemicals on their skin and that guidance for limiting such exposures was needed. However, because detailed guidance was precluded by a lack of measurement techniques, so was the ability to relate the risk of skin exposures to chemicals in a quantifiable manner. Attention focused instead on inhalation hazards, also a problem, and the development of air-sampling techniques to which quantitative analytical methods could be applied. With these air-sampling methods in hand and the ability to quantify exposures, establishing acceptable concentrations based on toxicological data and empirical workplace exposure outcomes was a natural progression.

In 1940, the Subcommittee on Threshold Limits was founded at the third annual meeting of the National Conference of Governmental Industrial Hygienists in Bethesda Maryland (ACGIH, 1984). The skin notation was first used by the American Conference of Governmental Industrial Hygienists (ACGIH®) in 1961 to indicate that a 'liquid compound can penetrate the unbroken skin to cause systemic effects' (ACGIH, 1984). The notation was not to be applied to chemicals that would result solely in dermatological effects. Also, the skin notation did not include any particular guidance on how to measure or assess the magnitude of risk, or the possible appropriate actions to take to reduce exposures. Today, some 24% of chemicals with a Threshold Limit Value (TLV®) have a skin notation. If one were also (i) to consider the far greater likelihood of a systemic health risk when the exposure were to damaged skin, (ii) to include those chemicals

that primarily injure the skin, and (iii) to consider the far greater number of possibly toxic chemicals for which an occupational exposure limit has not been assigned, and which therefore have not been given a skin notation, then the potential magnitude of the risk associated with skin contact becomes apparent.

That acute poisonings occur at all after skin contact in itself indicates the capability for substantial percutaneous uptake. It should also be obvious that less intense, but not acutely toxic, exposures probably occur frequently as well. In this context, compounds that bioaccumulate and have been associated with chronic adverse effects should be of special concern. These effects may range from debilitating illnesses manifested by neurological and behavioral effects, to often fatal conditions, such as cancer. However, long latencies, mixed exposures and undocumented skin exposures have prevented a verification of these effects, as far as workplace exposures are concerned. Most epidemiological studies fail to even mention the potential contribution from various routes of exposure, let alone document their magnitude. If skin absorption contributed to a fraction of the estimated total annual 60 000 deaths and 860 000 occupational illnesses attributed to workplace exposures in the US alone, it would be a substantial number (Leigh, 1997).

In spite of the multiple obstacles in making an association between skin exposures and disease, there are some clear examples of this connection. For instance, Fiorito *et al.* (1997) concluded that 'dimethylformamide can cause liver disease even if air TLVs are respected, because accidental [skin] contact with liquid DMF can significantly increase DMF uptake. In this situation, air monitoring is no longer sufficient to evaluate worker exposure.' Many other examples occur in the literature that demonstrate the skin route as the predominant means of exposure, resulting in adverse health consequences. Among these examples are nitroglycerin use in munitions manufacturing and associations with cardio-

vascular disease (Stayner *et al.*, 1992), and organophosphate pesticide exposure and acute and chronic neurological health effects (Baker *et al.*, 1978; Brown *et al.*, 1989; Srivastava *et al.*, 1991). Several reports have documented hepatic effects among workers after topical exposure to the aromatic amine methylenedianiline. Symptoms included pain, fever and jaundice (McGill and Motto, 1974; Williams *et al.*, 1974). Skin exposure to acrylamide-containing grout was associated with peripheral neuropathies among tunnel workers (Hagmar *et al.*, 2001). Transcutaneous absorption of ethylene glycol monomethyl ether, temporarily used as a cleaning agent, resulted in two cases of encephalopathy in a textile printing plant (Ohi and Wegman, 1978). These are just a few of the published examples where skin contact resulted in disease. It is very likely that there are many other cases that have occurred which have not been documented in the literature.

Most of the intoxication reports presented above have one thing in common. The exposures were to chemicals that have a relatively low vapor pressure. In fact, 81% of the chemicals with a TLV that carry the skin notation, and for which vapor pressure was available, have a vapor pressure <5 mmHg. These chemicals tend to remain on surfaces longer, as well as on the skin longer if contact occurs. Recent trends towards substituting chemicals into manufacturing processes that are less volatile in order to reduce air concentrations have quite likely increased the number of exposures that are primarily to the skin. These trends, together with good process controls, have been successful in reducing exposures to workers through inhalation. However, substituting lower-volatility chemicals and better control of airborne contaminants has increasingly made skin exposures more predominant and significant in the workplace.

Dermatitis has long been reported as the primary occupational illness associated with chemical exposures. The costs of dermatitis can include medical treatment, lost time, reduced productivity, loss of skilled labor, retraining, reduced earnings, workers' compensation claims and additional administrative duties. Penalties may also be incurred if an employer is deficient in complying with national health requirements. For example, in Denmark between 1979 and 1989, contact dermatitis accounted for 41% of all recognized cases of occupational disease. Of the total cases of dermatitis, 64% resulted in compensation for permanent injury, and 11% resulted in compensation for loss of earning capacity (Halkier-Sorensen, 1996).

Dermatitis cases far exceed the number of cases involving the pulmonary system in many industries. In industries such as printing, metal machining and treatment, food preparation, painting, beautician services and health care, the incidence of skin

complaints is many times higher than pulmonary complaints. Other industries, such as agriculture, also experience disproportionately more dermatitis. The true incidence of occupational dermatitis has been estimated to be perhaps 50-fold greater than is typically reported (Mathias, 1985). Once a worker is affected, the long-term prognosis is typically poor (Hogan, 1994). There also seems to be a direct association between higher medical and compensation costs and delayed referral to physicians (Shmunis and Keil, 1983). Early effort to identify, assess and control such skin exposures could probably prevent the majority of occupational dermatitis. Because dermatitis and systemic toxicities resulting from skin exposures are preventable, not doing so aggressively would be truly a disservice to public health.

Occupational exposure limits are based on diverse and usually incomplete toxicological experimentation. Protocols used to determine toxic effects most commonly involve acute, high-concentration dosing. These studies do little to predict the chronic effects of long-term exposures to chemicals, such as may typically occur through skin absorption. As in oral dosing, the bolus dose may not be substantially absorbed or may be primarily eliminated through the urine or feces. Toxic effects may be much more pronounced after repeated lower-dose exposures. For example, ammonium perfluorooctanoate is a surfactant used in the polymerization of fluorinated monomers. The acute dermal lethal dose (LD<sub>50</sub>) was found to be 7000 mg/kg for male rats. On the other hand, in subchronic dermal treatment, the lowest observable adverse effect level (LOAEL) was 20 mg/kg (Kennedy, 1985). For many compounds, absorption is substantially slower through the skin, allowing time for partitioning into critical fat-rich organs. A good example of this phenomenon was reported by Qiao and Riviere (2001), who demonstrated twice the target organ deposition from a single topical dosing of tetrachlorobiphenyl compared to an intravenous administration. This deposition is also predictable by pharmacologically based kinetic modeling of a dermally absorbed dose (McDougal and Boeniger, 2002).

Occupational skin exposures will remain significant occurrences for some time because of the present general lack of understanding among occupational health specialists about the risks. Research and a wide dissemination of relevant information on this topic should contribute significantly to future disease prevention from the dermal route of exposure.

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