Review

Manganese in Occupational Arc Welding Fumes—Aspects on Physiochemical Properties, with Focus on Solubility

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Physicochemical properties, such as particle sizes, composition, and solubility of welding fumes are decisive for the bioaccessibility of manganese and thereby for the manganese cytotoxic and neurotoxic effects arising from various welding fumes. Because of the diverse results within the research on welding fume solubility, this article aims to review and discuss recent literature on physicochemical properties of gas metal arc welding, shielded metal arc welding, and flux-cored arc welding fumes, with focus on solubility properties. This article also presents a short introduction to the literature on arc welding techniques, health effects from manganese, and occupational exposure to manganese among welders.

BACKGROUND

Arc welding processes and their applications

In Europe, approximately 730 000 full-time jobs concern welding and 5.5 million other jobs are related to it. In Sweden, there are approximately 25 000 full-time welders and additionally 250 000 jobs related to welding (Swedish Welding Commission, personal communication). The total amount of fume emitted from the welding industry worldwide has been estimated to 5000 tons per year (Redding, 2002). Welders constitute a very heterogeneous working population concerning type and quantity

of exposure, and health effects caused by welding fumes depend on a vast number of factors such as fume composition, concentration of various metals, solubility of each component, particle size distribution, and so on (Antonini et al., 1996, 1999; Fireman et al., 2008). Many of these factors depend on site-specific properties, such as temperature, moisture, and air exchange, and method-specific properties, such as welding method, welding consumables, voltage, and wire speed (Hovde and Raynor, 2007). Airborne particle concentrations vary because these welding parameters affect the fume generation to various extent (Gray and Hewitt, 1982; Dennis et al., 1997; Zimmer et al., 2002).

The most common industrial methods, presented in Table 1, are shielded metal arc welding (SMAW), gas metal arc welding (GMAW), flux-cored arc

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Table 1. Arc welding processes and applications (Eriksson, 2011).

Process	Synonyms	Applications
SMAW	Stick welding Manual metal arc welding	Welds all ferrous metals
GMAW	Metal inert gas welding Metal active gas welding Metal cord arc welding	Top quality welds in all metals and alloys in industry No slag produced in weld
FCAW		Deep penetration
Submerged arc welding	Unter Pulver Schweissung	High welding speed High metal deposition rates Deep penetration
GTAW	Tungsten inert gas welding	Top quality welds in all metals and alloys in industry No weld splatter No slag produced in weld

welding (FCAW), and gas tungsten arc welding (GTAW) (Stern et al., 1986; Burgess, 1991; Kura and Mookoni, 1998; Antonini et al., 2006a). These techniques make up 80–90% of all manufacturing and maintenance welding. SMAW is the single most common welding process worldwide (American Welding Society, 1995). However, in Sweden and Europe, GMAW presently makes up more than 50% of the market for consumables, FCAW approximately 22%, and SMAW approximately 15% (A. Eriksson, personal communication). The majority of all welding worldwide (Beckett et al., 1996) as well as in Sweden (A. Eriksson, personal communication) is performed using mild steels (MS), carbon steels, and low alloy steels, whereas welding in stainless steel (SS), aluminum, titanium, nickel, and other metals account for less than 10% of all welding (Beckett et al., 1996).

Manganese is found in all mild steels and is always used in steel alloys to improve metallurgical properties by neutralizing the effects of sulfur and preventing the oxygen from contaminating the molten metal (Burgess, 1991; Voitkevich, 1995; Barceloux, 1999). To restore the manganese lost by the heat during welding, manganese up to 15% by weight can be used as flux agents in the coatings of SMAW electrodes and FCAW electrodes (Villaume et al., 1979). Depending on the above mentioned factors, manganese generally makes up from 0.2% to 10% of the fume (American Welding Society, 1979; Arnold, 1983; Burgess, 1995). However, special steels, such as Hadfield steel and 13% Mn steel (A. Eriksson, personal communication), may produce higher concentrations of $MnO_2(s)$ in the welding fume (Moreton, 1977). In addition to $MnO_2(s)$, manganese can be present as $MnO(s)$, $Mn_3O_4(s)$, in various form of mixed metal oxides, such as $MnFe_2O_4(s)$ (Lucchini et al., 1995; Agency for Toxic Substances and Disease Registry, 2000; Hudson et al., 2001) or

as silicates (Sowards et al., 2005; Maynard et al., 2004). In addition, many consumables, that is, flux-cored electrodes used in FCAW and SMAW, contain also fluoride, so that several manganese fluorides are present in such welding fume, such as MnF_2 and $KMnF_3$ (Voitkevich, 1995).

Health effects from inhaled manganese and its relation to welding fume particles

Manganese is a trace element that is essential for normal development and body function across the life span of all mammals. As a divalent ion, it binds to and/or regulates many enzymes throughout the body; it is a required cofactor for arginase, which is responsible for urea production in the liver, for superoxide dismutase (Mn-SOD), which is critical to prevent against cellular oxidative stress, and for pyruvate carboxylase, an essential enzyme in gluconeogenesis. Thus, manganese deficiency, although not very often reported, has been associated with a variety of diseases in humans (Keen et al., 2000).

Of more frequent toxicological concern is manganese overexposure. Inhaled manganese can lead to adverse health effects including damage to the lungs, liver, kidney, CNS, and also a higher risk of infertility in case of male workers. Common homeostatic processes are normally capable of preventing manganese overload for a typical dietary intake, but in environments with chronic and excessive occupational exposures, these regulatory processes cannot maintain tolerable levels of the metal (Roth, 2009). As a consequence, prolonged occupational exposure to concentrations more than $1\,mg\,m^{-3}$ has been associated with an increased risk of neurological disorders and the development of a form of Parkinsonism known as manganism (Montgomery, 1995; Feldman, 1999; Kirkey et al., 2001; Olanow, 2004; Sriram et al., 2010). Moreover, recent evidence suggests that individuals with liver dysfunction and those

receiving parenteral nutrition exhibit many of the same symptoms as occupationally exposed workers (Roth, 2009). Recent studies suggests that chronic exposure to manganese levels below $0.5\,mg\,m^{-3}$ leads to more subtle effects on learning, memory, and behavior, such as tremor, weakness, reduced hand–eye coordination, and psychological impairments (Fitsanakis et al., 2006; Klos et al., 2006; Aschner et al., 2007; Bowler et al., 2007 Wastensson et.al., 2011). In the case of welders, neurological and neurobehavioral deficits, such as changes in mood and short-term memory, altered reaction time, and reduced hand–eye coordination, may occur when workers are exposed to levels of manganese less than $0.2\,mg\,m^{-3}$ in welding fumes. Affected workers frequently show abnormal accumulations of manganese in two areas of the brain, called "globus pallidus," which plays an important role in movement regulation, and "substantia nigra" (Olanow et al., 1996; Pal et al., 1999). These two areas of the brain are normally associated with the highest divalent metal concentrations. Manganism is associated with neuronal loss primarily in the globus pallidus (Olanow et al., 1996; Pal et al., 1999).

In addition to neurological disorders, it has been suggested from animal studies that manganese is a pulmonary irritant that can induce inflammation (Lison et al., 1997; Rice et al., 2001; Dorman et al., 2005). Several studies also show that full-time welders often experience some type of respiratory disorder during their employment, such as metal fume fever, bronchitis, lung function decrements, increased susceptibility to infection, and a possible increase in incidence of lung cancer (Sferlazza and Beckettt, 1991; Martin et al., 1997; Antonini et al., 2003, 2004). It has been found that inhalation to dust with high concentrations of the manganese oxides $MnO_2(s)$ and $Mn_3O_4(s)$ can cause an inflammatory response in the lung that eventually can result in impaired lung function and increased susceptibility to infections. However, this effect might be characteristic of respirable particulate matter (PM) in general and thus not depending solely on the manganese content of the particles (see Williams-Johnsson, 1999, and references therein). Of the pro-inflammatory metals, manganese was found to be the second most effective metal, after copper, in a study on inflammation in lung tissue and thus more effective than Ni, V, Fe(II), and Zn (Rice et al., 2001). Epidemiological studies have shown that individuals exposed to high levels of manganese, such as welders, does show increased frequency of respiratory distress, including pneumonia, bronchitis, and impaired pulmonary function (Bencko and Cikrt, 1984; Roels, et al., 1987; Saric and Piasek, 2000).

Studies on nasal toxicity and olfactory uptake of metals indicate that the sense of smell may be augmented after exposure to manganese compounds. Mergler et al. (1994) reported lower smell thresholds in manganese-exposed workers compared with controls. Lucchini et al. (1997) observed that smell thresholds in manganese-exposed workers decreased with increasing urine manganese levels. These findings may reflect accumulation of manganese in the olfactory bulb (Sunderman, 2001, and references therein) and may be of great importance for the uptake of manganese in the brain because olfactory receptor neurons contact directly both the external environment and the brain. However, the importance of this system in contributing to the overall human neurotoxicity of manganese via inhalation is not known (Antonini et al., 2006b).

Properties such as particle size distribution, surface area, surface morphology, and solubility determine the interaction of particles/aerosols with the surrounding environment and thereby accounts for its toxicity. Although no single property of a particle alone can describe its toxicity, the particle surface composition seems to be decisive for the interaction with biological systems (Midander, 2009). Moreover, the total surface area is important since it determines the interfacial area of the particle potentially in contact with a specific medium, such as epithelial cell walls. Consequently, from several toxicological studies, dose–response relationships were found to be stronger if the dose was expressed as surface area of the particles rather than mass (Oberdörster, 2000; Brown et al., 2001; Stoeger et al., 2006). According to Oberdörster et al. (2007), it should be stressed that the surface area concept should be considered in the context of particle surface properties such as chemistry, charge, coating, crystallinity, porosity, and reactivity. Anyhow, the impact from surface area on the dose–response relationship has been discussed and criticized (Wittmaack. 2007). Since particle size and size distribution decide the total surface area, these parameters are also crucial to understand the impact of surface area on the particle reactivity. Not surprisingly, surface reactivity has been found to increase with decreasing particle size (Oberdörster et al., 2005; Roduner, 2006).

Because the deposition of particles in the airways depends on the factors mentioned above, the distribution of respirable agglomerated particles in welding fume is of outmost importance concerning health effects of welding fumes (Hewett, 1995; Jenkins and Eager, 2005) as is the solubility of the agglomerated particles. In several studies, it has been suggested that soluble transition metals

in welding aerosols (Smith et al., 2000; McNeilly et al., 2004; Donaldson et al., 2005; Antonini et al., 2005) or in other PM (Hetland et al., 2000; Jiménez et al., 2000) might be a primary inducer of airway oxidative stress and inflammation. McNeilly et al. demonstrated that the pro-inflammatory effects of welding aerosol were entirely driven by oxidative stress arising from the soluble transition metals, and similar studies by Smith et al. as well as Antonini et al. have supported such conclusions. However, recent reviews on oxidant mechanism derived from particles (González-Flecha (2004)) show that these data are in conflict with evidence from other studies, i.e. that metal removal from PM does not necessarily affect the oxidative properties of PM. Moreover, some recent studies indicate that earth metals can up-regulate inflammatory genes (Drynda et al., 2009).

Iron and manganese share many biological protein transporters due to the similarity of the two metals, i.e. both are first-row transition metals with similar atomic masses, radii, and electron structure, they exist in multiple oxidation states, they have similar electro negativity, and their initial ionization energies are comparable. The interaction between manganese and iron is evident considering nutritional status. Iron status is crucial for the absorption of manganese, i.e. increased uptake of manganese is associated with anemia (Rossander-Hulten et al., 1991), whereas on the other hand excess of iron in the body have been found to suppress the uptake of manganese (Fitsanakis et al., 2006; Heilig et al., 2006; Thompson et al., 2007). Workers with iron deficiency may therefore be at greater risk of manganism than workers with higher iron levels. This might contribute to the controversy regarding the role of inhaled manganese in the causation of neurological effects associated with occupational exposures, especially among welders, generally having a parallel exposure of iron (Furbee, 2011). Santamaria et al. (2007) concluded that available data did not support association between welding and clinical neurotoxicity, although manganism was observed in highly exposed workers.

Transportation of manganese into the cell and distribution into the brain

Inhaled manganese is thought to be transported into the cells via several mechanisms. At present, four main transport mechanisms has been proposed (as reviewed by Roth et al., 2009), of which one can transport trivalent manganese, i.e. the transferrin (Tf)-dependent pathway. This pathway together with the Tf-independent pathway requires a divalent metal transporter protein called DMT-1. Since DMT-1 only transports divalent metal ions, any trivalent ions Mn^{3+} ions bound to transferrin must be reduced before complexation with DMT-1. Such a reduction has not yet been directly proven, either by ferric reductase (which reduces Fe^{3+} to Fe^{2+} before transportation into the cell) or by any other available reduction enzymes (Roth et al., 2009). On the basis of oxidation studies of Mn^{2+} in serum, strong implications of a redox process has however been made by Harris et al. (1994). Divalent manganese can also be transported into cells via the voltage-regulated Ca^{2+} channel and glutamate receptor Ca^{2+} channel. Once inside the cell, manganese is transported into the mitochondria via the Ca^{2+} uniporter and interferes with the ATP production, eventually causing disruption of mitochondrial function (Roth et al., 2009).

The entry of manganese into the brain can occur via three known pathways: through the capillary endothelial cells of the blood–brain barrier (BBB), by the choroid plexus of the blood–cerebrospinal fluid barrier (Crossgrove et al., 2004), or via the olfactory nerve from the nasal cavity directly to brain (discussed shortly in the Health Effects from Inhaled Manganese and Its Relation to Welding Fume Particles section). For occupational exposures, this latter route, sometimes called the *nose–brain barrier*, might be of great concern (Sunderman, 2001).

Occupational exposure to manganese in GMAW, FCAW, and SMAW fumes

Traditionally, occupational exposure measurements of manganese in welding fume have been made by collecting either or both of the two dust fractions "total dust" and "respirable dust" by personal sampling and thereafter analyzing the content of manganese in each fraction. On the basis of the findings from several studies that welding fume particles has mass median aerodynamic diameter (MMAD) between 0.2 and 0.6 µm, with less than 10% (GMAW) or 30% (FCAW) of the fume mass being larger than 1 µm, most of the particles from pure welding operations can be expected to be respirable.

For this paper, The Welding Institute (TWI, 2011) online database was extracted for manganese in GMAW, FCAW, and SMAW workplace air on the basis of personal measures from 315 measurements in the UK, Canada, and USA between 1973 and 2007 (Table 2). In addition, a Dutch welding fume database (DWFD) including measurements in the Netherlands from 1983 to present was extracted. The amount of manganese data was found to be limited to 108 measurements and restricted to one study from

Table 2. Concentration of manganese (mg m^{-3}) in GMAW, FCAW, and SMAW in personal samples of total or respirable dust.

Method	n	AM ± 95% CI	GM	Range	SD	Reference
GMAW[a]	262	0.134±0.020	0.057	0.001–1.06	0.167	TWI (2011)
GMAW[a]	16	0.1443±1.120	0.0470	0.0011–0.7780	2.0993	DWFD (2011)
GMAW[b]	11	0.100±0.049	0.11	0.051–0.192	0.069	Wallace et al. (2001)
GMAW[c]	42	0.5±0.3	0.2	0.01–4.93	0.9	Korzcynski (2000)
GMAW	58		0.131	0.007–1.510		Ellingsen (2006)
GMAW[a)]	89	0.21±0.04	0.16	0.01–1.47	0.20	
GMAW	20	0.1	0.08	0.01–0.3		Swedish Work Environment Authority (2000)
FCAW[a]	23	0.126±0.05	0.076	0.006–0.38	0.115	TWI (2011)
FCAW	20	0.468±0.787	0.556	0.072–4.370	1.641	Wallace et al. (2001)
FCAW	27	0.178±0.847	0.144	0.027–0.367	2.10	Smargiassi
FCAW	29		0.019	0.003–0.265		Ellingsen (2006)
SMAW[a]	30	0.080±0.053	0.04	0.01–0.7	0.140	TWI (2011)
SMAW[a]	25	0.0262±0.6038	0.0077	0.0007–0.3313	1.4331	DWFD (2011)
SMAW	61	0.20±0.07		0.0005–1.3105	0.28	Susi (2000)
SMAW	24	0.138±0.045	0.106	0.010–0.477	0.104	Balkhyour (2010)
SMAW	9	0.124	0.097	0.045–0.300		Meeker (2007)
SMAW	90		0.121	0.004–4.620		Ellingsen (2006)
SMAW	20	0.138		0.038–0.198		Yuan (2006)
SMAW[b]	12	0.041		0.0015–0.120		Karlsen (1994)
SMAW	137 48 13	0.077±0.019 0.29±0.11 0.126±0.043		0.0004–0.740. 006–1.72 0.022–0.23	0.11 0.39 069	Flynn (2009)
SMAW	20	0.1	0.08	0.02–0.4		Swedish Work Environment Authority (2000)

n, number of samples; SD, arithmetic standard deviation; 95% CI, 95% confidence interval calculated for AM and using t-distribution.

[a] Most the samples were sampled during welding in MS or non–stainless steel.

[b] All samples were sampled during welding in SS.

[c] Approximately 90% of the samples were sampled during welding in non–stainless steel. The 8-h TWA for manganese in Sweden is set to 0.2 mg m^{-3} (total dust) and 0.1 mg m^{-3} (respirable dust), the former being the same as TWA set by OSHA and ACGIH but lower than TWA set by NIOSH (1 mg m^{-3}).

the year 1999 at a shipyard (H. Kromhout, personal communication). In the case of GMAW, calculated arithmetic mean (AM) and geometric mean (GM) were close to those for the TWI data. For SMAW, the data in DWFD represent the lowest manganese concentrations of all studies. The database also includes 41 personal measurements collected in the absence of welding activity at the shipyard. These measurements (AM = 0.0025 mg m^{-3}, GM = 0.0015 mg m^{-3}, min = 0.0007, max = 0.0256 mg m^{-3}) are not included in Table 2. The TWI data base has been used for similar purposes in other studies, applying more specific criteria than those in the present paper. Flynn et al. (2009) presented mean manganese exposure for boilermakers (0.26 mg m^{-3}), pipefitters (0.08 mg m^{-3}), and ironworkers (0.12 mg m^{-3}). Overall data

are presented as SMAW in Table 2. Generally, the levels of fume exposure measured behind the helmet are lower than those measured external to it. However, the authors found no such correlation with regard to manganese concentration in the samples extracted from these databases.

On the basis of the studies presented in Table 2, exposure to manganese from GMAW fumes could be expected to vary from 0.001 mg m^{-3} (DWFD, 2011) to 4.93 mg m^{-3} as an extreme (Korzcynski et al., 2000), with typical concentrations in the range 0.05 to 0.25 mg m^{-3}. Exposure from FCAW fumes could be expected to vary from 0.003 mg m^{-3} (Ellingsen, 2006) to 4.370 mg m^{-3} as an extreme (Wallace et al., 2001), with typical concentrations in the range 0.08 to 1.2 mg m^{-3}. Exposure from SMAW

fumes could be expected to vary from 0.0007 mg m^{-3} (DWFD,2011) to 4.620 mg m^{-3} as an extreme (Ellingsen, 2006), with typical concentrations in the range of 0.03 to 0.4 mg m^{-3}. In a comprehensive review, Burgess (1995) suggested the range of exposure for manganese in GMAW to 0.01–0.05 mg m^{-3}, FCAW to 0.02–2.0 mg m^{-3}, and SMAW to 0.01–1.0 mg m^{-3}. Thus, FCAW fumes generally seem to contain highest concentrations of total manganese (soluble and insoluble), whereas GMAW fumes seem to contain lowest concentration. From some studies, it can be depicted that, irrespective of welding method, there is on average higher concentrations of manganese in welding fume from MS welding than SS. Extracting DWFD results in AM of 0.049 and 0.0096 mg m^{-3} for MS and SS, respectively. In a recent study from the Swedish Environmental Research Institute, IVL (2006), a similar result was found (see Table 3). However, the calculations in Table 3 are based on relatively few measurements.

The measured exposure ranges of manganese for welders should be taken into the context that chronic exposure to manganese levels below 0.5 mg m^{-3} have been suggested to affect learning, memory, and behavior and that even exposure levels below 0.2 mg m^{-3} in welding fumes can cause neurological and neurobehavioral deficits, such as changes in mood and short-term memory, altered reaction time, and reduced hand–eye coordination. On the basis of historical and present exposure measurements only, professional welders using FCAW seems to be at highest risk for developing these symptoms.

METHODS

Literature search was conducted in ISI Web of Knowledge and PubMed (NCBI). The search terms included the following (with "and," "or"): welding fume(s), manganese, physiochemical, particle size distribution, particle morphology, manganese solubility, occupational exposure, manganese homeostasis, manganese toxicity. Peer-reviewed articles on physicochemical properties with emphasis on solubility from 1994 to 2011 (also before 1994 for studies on particle size) were evaluated with regard to quality and relevance, i.e. the type and quality of solubility study, or particle surface study. In the case of studies on occupational exposure measurements, data on personal measurements of good quality were included, whereas most results based on static/stationary measurements were excluded. In a few cases, data from reports, i.e. not peer reviewed, have been cited (IVL and Swedish

Work Environment Authority). In addition, two welding data bases were extracted for manganese occupational exposure data. TWI online database was extracted for each of the welding techniques GMAW, FCAW, and SMAW. Data were divided according to welding technique only. Samples not specifically identified as breathing zone samples were excluded; otherwise, no other exclusion criteria were made. For the samples listed as below a detection limit, the numerical value for exposure was set to half this limit. In addition, DWFD was extracted with similar criteria.

FORMATION, COMPOSITION, MORPHOLOGY, SURFACE AREA, AND SIZE DISTRIBUTION OF PARTICLES FROM GMAW, FCAW, AND SMAW FUME

Fume generation

Welding fume is generated during transfer of molten metal from the electrode to the base metal because of the oxidation and condensation of the high-temperature metal vapor released into the air from the welding arc. The droplets from the electrode can be transferred to the metal welding substrate either as globular droplet or as spray droplet (Isaxon, 2008). The GMAW process uses automated and continuous electrode wire feed and an inert or active shielding gas, called *metal inert gas* or *metal active gas*. The shielding gas protects the molten metal from air oxidation by creating a microclimate around the welding point. The choice of shielding gas also depends on the substrate; with nonferrous substrates, inert gases are being used, whereas with ferrous substrates, argon mixes are being used. A welding process is often optimized by using a mixture of inert and active gases. Other than iron, a GMAW electrode may contain manganese, silicon, aluminum, and/or titanium to protect the welding material from oxidation (Isaxon, 2008). In SMAW, instead of using shielding gases, fluxing compounds are incorporated into the electrode to provide a shielding environment during the welding process. Welding fumes formed during processes in which fluxes are being used have been observed to be both chemically and physically more complex than fumes formed from GMAW processes (Antonini et al., 1999; Zimmer and Biswas, 2001; Jenkins, 2003). However, because of the enormous variation from between manufacturers, and from electrode to electrode in fluxing compounds, comparisons of fume composition of both SMAW and FCAW are very complicated (*Welding Handbook*). FCAW has

characteristics of both SMAW (a flux is used) and GMAW (a wire is used, although in FCAW it consists of a steel electrode surrounding a powder fill material). The flux are quite complex and include gas formers, deoxidizers, binders, slag formers, arc stabilizers, and alloying additions. In FCAW, the flux is found in the tubular wire, whereas it is applied to the outer sheath in SMAW (American Welding Society, 1979). GTAW is a fully manual process that uses a nonconsumable tungsten electrode, a shielding gas, and a separate filler material (Antonini, 2003).

Jenkins (2003) found that arc welding causes approximately 10% of the consumable welding electrode to vaporize. Most of the vapor recondenses in the weld pool, but approximately 10% condenses into metal oxide nanoparticles that aggregate into submicron clusters. Thus, from several studies, it has been found that the primary source of welding fume is droplets of molten wire from the consumable electrode (Voitkevich, 1995; Taylor et al., 2003), contributing to around 80–95% of the fume (Stern et al., 1986; Antonini, 2003), whereas the weld pool accounts for less than 10% of the total welding fume (Kura and Mookoni, 1998). There are also droplets of weld metal expelled during the welding operation; if too large to remain airborne, they are called spatter, but if smaller than 20 µm, they are called microspatter or sputter. Jenkins (2003) found that FCAW fume contains approximately 30% microspatter by mass, whereas GMAW fume consists predominantly of particle agglomerates smaller than 1 µm, and only 10% microspatter, i.e. particles larger than 1 µm. FCAW have been found to generate more fume than GMAW, and the composition of fumes generated from FCAW depends on the composition of the inner flux as well as tubular wire, and, to a minor extent, on the base metal (Wallace et al., 2010).

The fume formation rate depends on the welding process itself (e.g. welding current/voltage, arc length, type of shielding gas), composition of the consumable, and geometry of the weld and of the consumable (Villaume et al., 1979; Stern et al., 1986; Voitkevich, 1995; Antonini, 2003; Quimby and Ulrich, 1999). Fume formation rates for GMAW have been studied by Zimmer and Biswas (2001) and was found to vary between 0.035 and 0.37 g min^{-1}. More and smaller particles are formed with spray droplet transfer than with globular droplet transfer (Jenkins et al., 2005a). It has also been found that using pure CO_2 as shielding gas increases the fume formation rate significantly compared with a mix of Ar, CO_2, and O_2 (Zimmer at al., 2002). CO_2 can work as a source of oxygen at the high temperatures present and will then contribute to the evaporation from the spray droplets (Redding, 2002). In addition, CO_2 causes larger droplets to form from the electrode, and larger droplets are more likely to evaporate. Jenkins 2003 suggested that fume formation rates of 10 mg fume per gram of wire is common.

Particle formation

Studies on particle formation mechanisms of welding fume have indicated that individual primary particles generated during welding quickly accumulate together in the air to form larger agglomerated particles (Hewett, 1995; Voitkevich, 1995; Zimmer and Biswas, 2001; Jenkins, 2003). It is therefore likely that the pulmonary deposition is determined by the aerodynamic size of the agglomerates rather than the size of single primary particles (Antonini et al., 2006a" or "Antonini et al., 2006b). The dominating aerosol formation mechanisms during GMAW are nucleation, where metal fume at high temperatures condenses to primary particles followed by growth through coagulation, i.e. primary particles collide and adhere to each other to make an agglomerate. In addition to primary particle–particle collisions, agglomerates can also be formed through particle–agglomerate collisions and agglomerate-agglomerate collisions (Antonini, 2003). The agglomerates have chainlike structures (Jenkins and Eagar, 2005; Zimmer and Biswas, 2001; Antonini et al., 2006a" or "Antonini et al., 2006b), partly because the primary particles are formed from the magnetic mineral magnetite, $Fe_3O_4(s)$. The size of the agglomerate depends on the concentration of primary particles in the air, which is a function of fume formation rate together with ventilation. It also depends on the time the primary particles are given to collide with each other. Thus, particle sizes vary greatly depending on the distance from the arc, particularly with SMAW and FCAW, because of the much higher fume formation rates compared with GMAW (Friedlander, 1977). Zimmer and Biswas (2001) noted that the number concentration decreases fourfold from a distance of 4.8 cm to a distance of 19.2 cm from the welding nozzle and that the number concentration for the smaller particles decreases substantially when residence time is increased because they are scavenged by larger ones through coagulation.

The size of the primary particle is determined solely by material's critical diameter of nucleation (i.e. by its volatility) and the supercooling effect of the surrounding environment. Because different metals evaporate at different rates at a given temperature, the temperature, and thereby also the particle size, will indirectly be an indicator of the chemical composition of the primary particle (Isaxon, 2008). Jenkins (2003) concluded that primary particles formed from

Table 3. Concentration of manganese (mg m^{-3}) in fumes from MS and SS in personal samples of total or respirable dust.

Welding material	n	AM ± 95% CI	GM	Range	STD	Reference
MS	61	0.0491 ± 0.50	0.0071	0.0007–0.7780	1.97	DWFD (2011)
MS/SS	15	0.0367 ± 0.016	0.0299	0.0036–0.100	0.029	IVL (2006)
SS	16	0.0096 ± 0.74	0.0043	0.0008–0.0531	1.28	DWFD (2011)
SS	15	0.0078 ± 0.030	0.0053	0.001–0.021	0.054	IVL (2006)

N, number of samples; STD, arithmetic standard deviation; 95% CI, 95% confidence interval calculated for AM and using *t*-distribution.

the same welding fume show compositional variations that depend on primary particle size. However, compositional variation from one primary particle to the next is averaged out once these primary particles aggregate into agglomerates, and there is no compositional variation with the size of agglomerates.

Morphology, surface area, and size distribution of particles

Welding fume particles are primarily fractal-shaped agglomerates with complex and nonuniform shapes and surfaces and a given sample might contain a wide distribution of particle sizes. The agglomerates are held together by electrostatic and van der Waal forces (Antonini et al., 2006a" or "Antonini et al., 2006b), and the magnitude of these forces is of toxicological relevance since interaction with the lung tissue and biological fluids can break the bonds in the agglomerates and make the primary particles dissociate. This causes the surface area of the aerosol to increase, and because the individual primary particles are in the ultrafine size range (0.01–0.10 µm), an increase in toxicity is possible (Isaxon, 2008). Moreover, smaller-sized particles generally show higher dissolution rates (Midander et al., 2007a, 2007b), which implies that the effective surface area is larger on smaller particles compared with coarser particles. Thus, an increase in toxicity due to increased solubility of smaller particles is possible as well. However, because of the properties mentioned, the surface area of welding fume particles cannot easily be estimated.

Aerosols generated during GMAW have been shown to be smaller and primarily arranged in homogeneous chainlike agglomerates (Jenkins, 2003), whereas aerosols generated during FCAW and SMAW are larger, more chemically complex and contain a mixture of chainlike and spherical structures. Zimmer and Biswas (2001) suggested that three modes of particle sizes can clearly be distinguished regarding fumes from GMAW and FCAW: a nucleation mode of individual particles from a few nanometers to about 0.1 µm, an accumulation mode (0.1–1 µm) of agglomerated, aggregated, and coalesced particles formed from the nucleation mode, and a coarse mode of unagglomerated particles in the range of approximately 1–20 µm. The latter category includes microspatter. Berlinger et al. (2011) suggested that, based on particle mass size distributions, no large differences between the welding aerosols from GMAW and SMAW (and tungsten inert gas welding) were found. The dominant range with respect to mass was found to be between 0.1 and 1 µm, regardless of the welding technique. However, the authors emphasized that the particle size distribution obtained by various kind of particle counters, counting agglomerated particles, is not the same as the primary particle size distribution determined by microscopic techniques, such as TEM. In the same study, most primary particles were found to have geometric diameters (equivalent projected area diameter) between approximately 5 and 40 nm, independently on the welding technique.

Particle size distribution from GMAW-SS has been determined by Antonini et al." or "Antonini et al., 2006b (2006a), who found that the most significant mass of particles, containing 85–95% of the total mass collected, was in the fine size range with cutoff diameters of 0.10–1.0 µm. Calculations indicated MMAD to be approximately 0.24 µm, considering only the fine size range (0.10–1.0 µm). MMAD of agglomerates from GMAW has also been studied by Zimmer and Biswas (2001), who reported 0.149 µm, thus having a high prevalence of being deposited in the alveolar region. Several other authors have proposed MMAD for GMAW and FCAW fumes to be in the range 0.2–0.4 and 0.3–0.4 µm, respectively (see Table 4). Moreover, particles generated from SMAW have been studied by Hewett (1995), who found that most particles had larger MMAD, i.e. 0.59 µm, than particles in GMAW-generated fume (0.46 µm). Again, one possible explanation is that SMAW have greater fume formation rates than GMAW. In that study, the specific surface area was found to be smaller for SMAW fumes than that for GMAW fumes, which is consistent with the fact that specific surface area is inversely proportional to the size of an agglomerate.

Table 4. MMAD of welding fume particles calculated from data obtained with cascade impactors.

Welding process	MMAD (µm)	Reference
SMAW	0.45–0.59	Hewett (1995)
SMAW	0.5–0.8	Bland (1973)
SMAW	0.35	Berner and Berner (1982)
SMAW	0.2	Eichhorn and Oldenburg (1986)
SMAW	0.3	Stephenson et al. (2003)
SMAW	0.5	Isaxon et.al (2009)
SMAW	0.3[a]	Berlinger (2011)
SMAW	0.6–0.8[b]	Sowards et al. (2005)
FCAW	0.3	Bland (1973)
FCAW	0.4	Heile and Hill (1975)
FCAW	0.43	Jenkins (2003)
FCAW	0.352	Zimmer (2001)
GMAW	0.24–0.33	Jenkins (2003)
GMAW	0.25	Hewett (1995)
GMAW	0.2–0.4	Bland (1973)
GMAW	0.3	Heile and Hill (1975)
GMAW	0.2	Eichhorn and Oldenburg (1986)
GMAW	0.3[a]	Berlinger (2011)
GMAW	0.2–0.3	Isaxon et.al (2009)
GMAW	0.149	Zimmer (2001)
GMAW	0.24	Antonini et al. (2006)

[a] Reported here as the mobility diameter of particles with highest number concentration.
[b] Reported here as the GMD of distributions.

Other studies report MMAD for SMAW fumes ranging from 0.2 to 0.6 µm (see Jenkins et al., 2005c and references therein).

On the basis of these studies, FCAW and SMAW particles typically have MMAD approximately 0.3–0.6 µm, whereas GMAW have MMAD approximately 0.2–0.4 µm. Particle sizes ranges from a few nanometers to 20 µm; however, less than 10% (GMAW) or 30% (FCAW) of the fume mass consists of particles larger than 1 µm. Moreover, MMAD seems to be less dependent on consumables used, i.e. MS or SS electrodes.

Chemical composition of arc welding fumes

The primary component of all welding fume is iron oxide, i.e. $Fe_3O_4(s)$ (Burgess, 1991, 1995). The presence of specific metals and their compounds in the fume depends on the physicochemical properties of the specific metals, such as vapor pressure and boiling point, but also on welding temperature, type of welding material, and concentration of metal in the electrode or welding material (Burgess, 1991). The relative concentration of elements in the fume is however very different from that in the consumable

because elements with lower boiling points such as fluorine and manganese are significantly enriched in the fume over their concentrations in the consumable and parent metals (Stern et al., 1986). Oxygen can form various metal oxides, such as $Fe_3O_4(s)$, $FeCr_2O_4(s)$, $K_2CrO_4(s)$, $K_2FeO_4(s)$, $K_2MnO_4(s)$, $MnFe_2O_4(s)$, $Na_2CrO_4(s)$, and $NiO(s)$ (Voitkevich, 1995), which normally are present as multiple ionic compounds, mixed together in the fume. In addition, X-ray diffraction studies have identified a variety of pure manganese-containing oxides in welding fumes, such as $MnO(s)$, $Mn_2O_3(s)$, and $Mn_3O_4(s)$. Minni et al. (1984) observed that Mn^{2+} and Mn^{3+} (as MnO and Mn_2O_3) are the most probable oxidation states of manganese in welding fume generated using SMAW-SS and GMAW-SS processes. Since many consumables, i.e. flux-cored electrodes used in FCAW and SMAW, contain also fluoride, most metals in welding fume can exist as both oxides and fluorides. Voitkevich (1995) demonstrated that the core of particles generated by MS electrodes was composed of an insoluble complex of iron and manganese in the forms of $Fe_3O_4(s)$ and $MnFe_2O_4(s)$. With flux-cored electrodes, the distribution of iron and manganese within the welding particles was more

complex. Soluble fluoride complexes, i.e. $K_3FeF_6(s)$, $FeF_3(s)$, $MnF_2(s)$, and $MnF_3(s)$, were concentrated at the particle surfaces, whereas the oxides $Fe_3O_4(s)$ and $MnFe_2O_4(s)$ were concentrated in the particle core (see Antonini et al., 2006a" or "Antonini et al., 2006b, and references therein). It has been found that, in the case of SMAW fume, which has a similar chemistry as FCAW fume, several metals were present to a large extent as fluorides (e.g., K, Na, Ca, or MnF_2) originating from the outer shell, whereas metal oxides (e.g., $Fe_3O_4(s)$) originated from the inside core portions (Jenkins, 2003). Konarski et al. (2003) showed that SMAW-generated particles are highly oxidized particles composed of a shell rich in chlorides, fluorides, silicates, and potassium, whereas the core is composed mainly of iron, chromium, and manganese oxides.

The total manganese content in welding fume has been studied quite extensively. Values between 5 and 15 mass% (Keane et al., 2010; Yoon et al., 2009; Berlinger et al., 2008; Hewitt, 1983) seem to be representative for average manganese levels in most welding fumes. One important exception is welding fumes from high manganese steel (J. M. Antonini et al., 2010) in which the SMAW-hard surfacing fume contained approximately 50 mass% manganese. It has been found that fumes generated from manganese-rich hard surfacing/hard facing rods have concentrations between 30% and 60%, depending on the type of rod. However, the relatively high concentrations in the GMAW-MS fume, i.e. 22%, found in the study by Antonini et al. (2010) remain unexplained (J. M. Antonini, personal communication).

SOLUBILITY OF MANGANESE CONTAINING PARTICLES

In vitro solubility of manganese containing particles derived from welding fumes

Studies by Voitkevich (1995) and Antonini et al. (1999) have shown that welding fume particles produced during GMAW is relatively insoluble compared with particles from SMAW and FCAW processes. Indeed, GMAW-SS particles have been observed to persist in the lungs for long periods of time (Al-Shamma et al., 1979; Antilla, 1986; Lam et al., 1979). The differences in solubility can to a large extent be explained by the fact that the core of particles generated by MS electrodes used in GMAW is composed of insoluble iron and manganese complex, whereas particles from SMAW and FCAW contain soluble forms of iron and manganese, such as the

fluorides $K_3FeF_6(s)$, $FeF_3(s)$, $MnF_2(s)$, and $MnF_3(s)$, concentrated at the particle surfaces (Voitkevich, 1995). The oxides of manganese, $MnO(s)$, $MnO_2(s)$, $Mn_2O_3(s)$, and $MnFe_2O_4(s)$ are insoluble in water at neutral pH (i.e. no solubility constants, K_{sp}, have been reported), whereas permanganates, such as potassium permanganate ($KMnO_4$), are easily soluble in water ($64\,g\,dm^{-3}$ at 20°C) as is manganese fluorides, such as MnF_2 ($10.5\,g\,dm^{-3}$ at 20°C) and manganese silicates. Moreover, it has been found that larger particles consist mainly of light elements such as Al, Si, K, Na, F, and water-soluble compounds, whereas smaller particles are predominantly composed of heavy metals such as Fe, Ni, Mo, Mn, Cr, and their oxides (Stern et al., 1986). For particle containing heavy metals, the reactivity of the surface of the smaller-sized particles, in terms of the release of specific metal ions, has been suggested to be higher compared with particles of larger size because of a thinner surface oxide film and an enhanced segregation of impurities at the surface (Nyborg et al., 1992). Midander et al. (2007a, 2007b) and Karlsson et al. (2009) found that iron is released to a larger extent to a solution from the surface as the particles decrease in size.

However, the solubility of metal compounds in fumes is not well characterized, and the definitions of "solubility," the media used for dissolution studies, and the analytical methods used to measure it are so diverse that it is difficult to compare data from different studies. "Solubility" is a thermodynamic term that gives information on the concentration of the solute at equilibrium and is, in the case of metal ions, a consequence of competition between various ligands in binding to the metal ion. There is no such thing as an "unbound" metal ion in solution; it is rather hydrated, as in the hexaaqua complex of manganese, $Mn(H_2O)_6^{2+}$. Furthermore, the term "soluble" can be misleading if the conditions such as kinetics, concentration, temperature, and solvent are not well defined. As will be discussed, in vivo solubility of welding fume particles will differ substantially from the solubility of the same particles in water or dilute acid solutions, as generally used in laboratory research. This will create inconsistency in the interpretation of the results from measuring soluble metals in welding fumes. This section will focus on studies of solubility of welding fume derived manganese in artificial biologic media or otherwise under conditions resembling physiological conditions (with respect to pH and temperature). Examples of artificial biologic media that has been used for solubility studies of welding fumes are presented in Table 5.

Several solubility studies of metal oxides in blood, artificial gastric fluid, and fluids mimicking various

Table 5. Specific artificial biologic media used for bioaccessibility studies of manganese in welding fume.

Test media	Notation	pH	Simulated environment	Description
Phosphate-buffered saline	PBS	7.4–7.6	Blood	A standard physiological solution that mimics the ionic strength of human blood serum. It is widely used in the research and medical health care community as a reference test solution for comparison of data under simulated physiological conditions
Gamble's solution	GMB	7.4	Lung epithelial lining fluid	Mimics interstitial fluid within the deep lung under normal health conditions (Stopford et al., 2003). Contains magnesium chloride hexahydrate, sodium chloride potassium chloride, dibasic sodium phosphate, sodium sulfate, calcium chloride dehydrate, sodium acetate trihydrate, sodium bicarbonate, and sodium citrate dehydrate (Moss, 1979)
Hatch's solution	HS	7.4	Artificial lung lining fluid	As GMB and also D-glucose, phosphatidylcholine, α-tocopherol, uric acid, serum albumin, lysozyme, apo-transferrin, ascorbate, and glutathione (Hatch, 1992)

Table 6. Welding fume manganese solubility in some relevant media.

Media type (pH)	Fume type	Extraction time, h (temperature, °C)	Total Mn (mass % of total metal)	Soluble Mn (mass % of total metal)	Reference
PBS (7.2)	GMAW-SS	2 (37)	7–15	0.2–0.9	Keane et al. (2010)
PBS (5.0)	GMAW-SS	2 (37)	7–15	2.6–9.3	Keane et al. (2010)
PBS (7.4)	GMAW-SS	24 (37)	23	0.4	Antonini (1999)
PBS (7.4)	GMAW-MS	24 (37)	15	1.9	Antonini (1999)
PBS (7.4)	SMAW-SS	24 (37)	17	4.4	Antonini (1999)
Gamble's (7.4)	GMAW-SS	0.5–24 (20)	7	0.64–1.1	Berlinger (2008)
Gamble's (7.4)	SMAW-SS	0.5–24 (20)	7.7	1.0–5.0	Berlinger (2008)
Hatch's (7.4)	GMAW-SS	0.5–24 (20)	7	2.7–14	Berlinger (2008)
Hatch's (7.4)	SMAW-SS	0.5–24 (20)	7.7	6.0–6.8	Berlinger (2008)
Water (~8)	GMAW-SS	0.5–24 (20, 37)	7	0.93–3.0	Berlinger (2008)
Water (~8)	SMAW-SS	0.5–24 (20, 37)	7.7	9.0–16	Berlinger (2008)
Water (~8)	FCAW-SS	1 (37)	7.24 ± 3.37	0.07–0.39	Yoon et al. (2009)
Water (~8)	FCAW-MS	1 (37)	8.19 ± 1.79	0.01–0.98	Yoon et al. (2009)
Water (7.4)	GMAW-MS	24 (37)	21.7	2.9	Antonini (2010)
Water (7.4)	SMAW-SS	24 (37)	50.9	0.6	Antonini (2010)
NH$_4$Ac (~4.6)	GMAW-SS	1 (37)	–	10	Berlinger (2009)
NH$_4$Ac (~4.6)	GMAW-MS	1 (37)	–	16	Berlinger (2009)
NH$_4$Ac (~4.6)	SMAW-SS	1 (37)	–	31	Berlinger (2009)
NH$_4$Ac (~4.6)	SMAW-MS	1 (37)	–	9.3	Berlinger (2009)

part of the expiratory region have recently been presented (Midander et al., 2007a, 2007b; Cronholm et al., 2011; Berlinger et al., 2011; Keane et al., 2010). An important key message from this type of research is that the solubility at specific conditions is decisive for metal oxides concerning the extent of metal release from such oxide particles. In Table 6, the results from studies on manganese solubility in some relevant media are presented.

Gamble's solution (GMB) mimics extracellular epithelial lining fluid found in alveoli (Moss, 1979). The epithelial lining fluid protects the epithelial surface of the lower respiratory tract from the damaging effects of oxidants (Stopford et al., 2003).

Hatch's solution (HS) simulates lung lining fluid (Hatch, 1992). Lung lining fluid is a primary constituent of the pulmonary host defense system and is distributed continuously throughout the respiratory tract, although its composition can vary between the conducting airways and alveoli. None of these solutions are acid enough (pH 7.4) to dissolve manganese oxides to any extent. The main difference in composition is that HS contains proteins, such as transferrin (Tf), glutathione, and albumin, which are important factors in the dissolution of manganese compounds. Berlinger et al. investigated the dissolution of manganese from GMAW-SS and SMAW-SS fumes in GMB, HS, and water at 20°C and 37°C, given extraction times from 0.5 to 24 h. The dissolution of manganese from GMAW-SS fume was much higher in HS (2.7–14% of total manganese) than that in GMB, in which manganese solubility was comparable to that in water (0.93–12% of total manganese). In all cases, an increase in solubility with time could be found. For SMAW-SS fumes, the solubility was highest in water and lowest in GMB (Berlinger et al., 2008). Unfortunately, no information on manganese speciation in the GMAW-SS fume was provided in the study. In 1970, Keefer et al. demonstrated that a single protein binds most manganese and iron in rat serum, and this protein was later suggested by Aschner and Aschner (1990) to be Tf. Molecular evidence was provided by Aisen et al. already in 1969. In that study, manganese was found to be coordinated in the trivalent state (Mn^{3+}), with two metal ions tightly bound to each Tf molecule. Later studies have confirmed that manganese binds to the Tf/Tf receptor system (Burdo et al., 2003; Rouault and Cooperman, 2006). In contrast to the findings that Mn^{3+} in serum is approximately 100% bound to Tf, thermodynamic modeling of divalent manganese (Mn^{2+}) in serum at pH 7.4 predicts that approximately 90% of Mn^{2+} is bound to serum proteins but that only approximately 1% is bound to Tf (Harris et al., 1994). Furthermore, the model predicts that Mn^{2+} under these condition also exist as a hydrated ion (6.4%), and in complexes with bicarbonate (5.8%), citrate (2.0%), and other small molecular weight ligands (1.8%).

In a study by Keane et al. (2010), GMAW-SS welding fumes was found to have a soluble manganese fraction in simple phosphate-buffered saline (PBS) both at pH 7.2 and 5.0 (simulating the pH and phosphate levels typical of cytosolic or lysosomal fluids in cells), with the highest fraction of soluble manganese, i.e. up to around 9%, at pH 5.0, and lowest, up to around 1%, at pH 7.2. In a study by Antonini et al. (1999), using a similar PBS, GMAW-MS, GMAW-SS, and SMAW-SS fume particles were suspended in PBS at pH 7.4 and incubated for 24 h at 37°C and centrifuged. Soluble metals were detected in the soluble fraction of the SMAW-SS, whereas the GMAW-MS and GMAW-SS fumes were found to be largely insoluble. In recent studies, Antonini et al. (2010) concluded that GMAW-MS fume was relatively insoluble in water (for 24 h at 37°C) with only 1.35% soluble metals, in which manganese made up 47.3% of the soluble fraction. The SMAW-SS fume was found to be highly soluble, with 19.4% of all metals in the soluble fraction. However, even if the percentage of total manganese was more than double (50.9%) in the SMAW-SS fume compared with GMAW-MS, the soluble fraction only contained 1.43% manganese. Significant amounts of soluble K and Na were present in the SMAW-SS fume. Yoon et al. (2009) found that FCAW-MS fume contain more metal in terms of total weight percent than FCAW-SS fume, i.e. approximately 51% versus 40%, with iron (~26%), manganese (~8%), magnesium (~8%), and sodium (~4%) being the four most abundant metals. However, the soluble metal content, as determined by incubation in distilled water at 37°C, was significantly higher in FCAW-SS welding fumes than that in FCAW-MS welding fumes (~16% versus 7%).

With the difficulties in interpreting the results from measuring soluble metals in welding fumes in mind, the effect of acidity on manganese solubility, i.e. the competition between protons and Mn-ions on binding to ligands, in such studies might still be seen comparing media that have similar properties, with no strong binding ligands, i.e. PBS, NH_4Ac, water and also Gamble's solution (table 6). In these media, the solubility of manganese from GMAW-SS fume seems to be considerably lower at pH levels higher than 7 (0.2–3 mass %) than that at pH levels 5 and lower (3–10 mass %). A similar result can be seen for GMAW-MS; at pH levels higher than 7, approximately 2–3 mass % is dissolved, whereas lower than pH 5, 16 mass % has been found. With the exception of the solubility in water, as presented in the study by Berlinger et al. (2008), a similar trend can be found for SMAW-SS fume, i.e. a higher solubility in media with lower pH value. The effect on solubility, due to complexation with ligands in the media, might be discerned if the solubility in HS is compared with the solubility in each of the other media, given the same pH, extraction time, and temperature. At pH 7.4, the manganese solubility for GMAW-SS in HS is 14% (extraction time 24 h). In the other media, the manganese solubility is 1.1% or less at pH 7.4 (extraction time 24 h). On the other hand, the solubility of manganese from SMAW-SS fume does not seem to be

higher in HS than that in the other media. There are, however, not enough data to establish these findings.

It can be noticed that the 24-h exposure of particles in artificial biological media is a "standard" time duration, which often enables comparison with existing metal release/dissolution data as well as acute toxicity data. According to Midander (2009), exposure time should be selected to be relevant for the exposure scenario being simulated. For example, the estimated time for the gastric phase of digestion is approximately 2 h, which was used for the artificial gastric fluid (Hamel et al., 1998), described in the next section. In a similar way, prolonged periods might be more relevant to simulate effects of particles of relatively stable or passive materials and for simulated lung environments, where particles can be trapped for a very long time (Midander, 2009).

In vitro solubility of manganese oxide containing particles derived from other sources

In vitro solubility studies of $Mn_3O_4(s)$ particles in GMB and HS have been made by Vitarella et al. (2000a). $Mn_3O_4(s)$ particles from bulk powder with MMAD of 0.73 µm, i.e. close to that of arc welding fume, were mixed with GMB and HS, respectively, corresponding to a manganese concentration of 40 µg ml^{-1} and incubated up to 192 h (8 days) at 37°C. Rate constants for dissolution and solubility concentrations (see Table 7) were measured and compared with those of $MnPO_4(s)$ particles and soluble $MnSO_4(s)$ particles. The solubility after 8 days for manganese from $Mn_3O_4(s)$ in GMB were 0.12 µg ml^{-1} (0.3%) and for HS 2.49 µg ml^{-1} (6.2%). Thus, manganese solubility in HS was 20 times greater than that in GMB. As discussed earlier, a similar result was found by Berlinger et al. (2008) for GMAW-SS, containing mostly insoluble manganese oxides, but

not for SMAW-SS, containing also water-soluble manganese fluoride particles (Table 6). There was much higher dissolution for the soluble $MnSO_4(s)$ and higher dissolution for slightly soluble $MnPO_4(s)$ compared to $Mn_3O_4(s)$ regardless of media (Vitarella et al., 2000a). The estimated dissolution rate constants for dissolution of manganese from $Mn_3O_4(s)$ particles in HS were found to be considerably higher than those in GMB. In addition, the dissolution rate constants for $MnPO_4(s)$ and $MnSO_4(s)$ were in the order of hundred to thousand times faster respectively than for $Mn_3O_4(s)$ (Vitarella et al., 2000a). It should be mentioned, however, that one difference between particles derived from welding fume and industrial manganese oxide is the coating of silicates or halides at the surface of the primary particles, and on the agglomerate as a whole, as described by Sowards et al. (2005) and Maynard et al. (2004). This should be taken into account when making comparisons, in terms of solubility, between manganese particles with different origin.
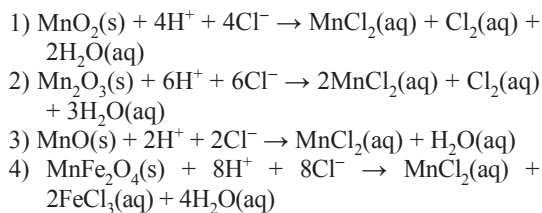
In a series of thorough studies on the release of copper, nickel, and iron from various oxides and alloys, Midander et al. (2007a, 2007b, 2009) found that artificial biologic media of similar pH but with various concentrations of ionic and organic compounds showed large variation in release patterns for the same material. Thus, the solubility of transition metal oxides, such as manganese oxides, from various particles, irrespective of its source, depends strongly on the presence of various proteins or other ligands in that media. Although out of scope for this review, it should be mentioned that in vivo studies of dissolution rates for and lung clearance of MnO_2, Mn_3O_4, $MnPO_4$, $MnSO_4$, and $MnCl_2$ particles in rodents are inconclusive. Dorman et al. (2001) showed that rodents exposed to $MnSO_4(s)$ for a specific time had lower

Table 7. Manganese oxide solubility in some relevant media.

Media type (pH)	Manganese source	Extraction time, h (temperature, °C)	Total amount of $Mn_3O_4(s)$	Dissolved amount of $Mn_3O_4(s)$	Reference
Trypsin (7.6)	Marine sediments	16 (20)	1480 µg g^{-1}	11 µg g^{-1}	Turner and Olsen (2001)
Pepsin (2.0)	Marine sediments	16 (20)	1480 µg g^{-1}	696 µg g^{-1}	Turner and Olsen (2001)
GI (pH 7.0)	Marine sediments	16 (20)	1480 µg g^{-1}	521 µg g^{-1}	Turner and Olsen (2001)
GI (pH 2.0)	Marine sediments	16 (20)	1480 µg g^{-1}	1190 µg g^{-1}	Turner and Olsen (2001)
NH_4Ac (7)	Marine sediments	16 (20)	1480 µg g^{-1}	220 µg g^{-1}	Turner and Olsen (2001)
Gamble's (7.4)	Powder	192 (37)	40 µg ml^{-1}	0.12 µg ml^{-1}	Vitarella (2000a, 200b)
Hatch's (7.4)	Powder	192 (37)	40 µg ml^{-1}	2.49 µg ml^{-1}	Vitarella (2000a, 200b)

lung manganese concentrations compared with similar exposure levels achieved following either $Mn_3O_4(s)$ or $MnPO_4(s)$ exposure (Vitarella et al., 2000b). However, several studies indicate that other absorptive factors, such as particle size and specific surface area, are also important for lung clearance, in addition to solubility and nonabsorptive factors (mechanical transport) (Vitarella et al., 2000a, Roels et al., 1997; Drown et al., 1986; Adkins et al., 1980). Mechanical transport has been suggested to be predominating for the less soluble forms of manganese salts, i.e. $Mn_3O_4(s)$ and $MnPO_4(s)$ (Vitarella et al., 2000a).

In addition to in vitro solubility studies of manganese oxides in artificial lung fluid, studies in gastric environment has also been undertaken. Artificial gastric fluid aims at mimicking the very acidic conditions in the stomach and can for example be composed of acidified pepsin (Turner and Olsen, 2001) or just diluted hydrogen chloride, giving approximately pH 1.5 (Hamel et al., 1998). Under such acid conditions, swallowed manganese oxide particles can potentially dissolve in the stomach. Disregarding complexation reactions with other ligands than chloride ions, the dissolution can be exemplified by the acid-driven reduction–oxidation reactions of trivalent and tetravalent manganese oxides (1–2) or by the acid-driven reactions of divalent manganese oxides (3–4) with hydrogen chloride:

1) $MnO_2(s) + 4H^+ + 4Cl^- \rightarrow MnCl_2(aq) + Cl_2(aq) + 2H_2O(aq)$
2) $Mn_2O_3(s) + 6H^+ + 6Cl^- \rightarrow 2MnCl_2(aq) + Cl_2(aq) + 3H_2O(aq)$
3) $MnO(s) + 2H^+ + 2Cl^- \rightarrow MnCl_2(aq) + H_2O(aq)$
4) $MnFe_2O_4(s) + 8H^+ + 8Cl^- \rightarrow MnCl_2(aq) + 2FeCl_3(aq) + 4H_2O(aq)$

According to Antonini" or "Antonini et al., 2006b et al. (2006b), insoluble welding particles that deposit in the tracheobronchial region are expected to have a short half-time in the respiratory tract due to removal by the mucociliary escalator, i.e. cilium that transports mucous up to the larynx. Depending on where in the tracheobronchial region the particle is located, this transportation takes approximately 0.5 to 5 h. Thus, unless dissolved, such particles will eventually be swallowed, processed, and later on presumably excreted from the body via the gastrointestinal (GI) tract (Antonini[AU: Please specify if this refers to "Antonini et al., 2006a."] et al., 2006b). The kinetics of manganese oxide dissolution from welding fumes in human gastric fluid has not yet been studied. However, the dissolution of manganese oxide in artificial gastric fluid, based on trypsin solutions (modeling intestine environment) and acidified (pH 2) pepsin solutions (modeling stomach/gut environment), has been studied for environmental purposes. Polluted marine sediments with known concentration of manganese oxide were mixed with appropriate amount of artificial gastric fluid under a digestion period of 16 h at 20°C. The dissolved amount of manganese was then compared with the dissolved amount of manganese from traditional extraction media, but also to natural GI fluid from fish (pH 7) and an acidified version of the same fluid (pH 2). The results showed that the amount of manganese dissolved by trypsin was about equal to the water-soluble fraction (1%), whereas approximately 50% manganese was available to the acidified pepsin media, and 35% to 80% was available to fish GI fluid under neutral and acidified conditions, respectively. On the basis of these results, the authors suggested that the extent of dissolved manganese by the enzymatic reagents indicates that ligands and/or functional groups present in gastric fluid are very important for the dissolution of manganese (see Table 7).

The uptake and translocation of manganese to the olfactory bulb, as studied with injections of dissolved manganese chloride ($MnCl_2$) in rats (Tjalve and Henriksson, 1999; Takeda et al., 1998; Gianutsos et al., 1997), has been suggested to involve complexation with the dipeptide carnosine (β-alanyl-L-histidine), which is present in comparable high concentrations in the olfactory bulb. Carnosine is known to bind Ni^{2+}, Cd^{2+}, Zn^{2+}, Cu^{2+}, and also divalent manganese in water solutions, forming stable water-soluble complexes (see Sunderman, 2001, and references therein). However, solubility studies of manganese oxides under conditions prevailing in the nasal tissues, olfactory receptors, or olfactory bulb has not yet been performed.

CONCLUSIONS, DISCUSSIONS, AND RECOMMENDATIONS FOR FUTURE RESEARCH

In contrast to literature on welding fume characterization and exposure, the literature on welding fume solubility is not comprehensive. As for now, only few solubility studies of manganese from welding particles in artificial biological media have been performed. The results of these studies are inconclusive, partly because the definitions of "solubility," media, and analytical methods used are so diverse. However, some trends might be seen from these studies. Fumes generated during GMAW processes tend to be mostly water insoluble (typically defined from incubation for 24 h in 37°C) and closely mimic

the metal composition of the welding wire that is consumed during the process, whereas fumes from SMAW processes tend to be highly water soluble, partly because of the presence of alkali metals (potassium and sodium) (Antonini, 1999), fluorides (Voitkevich, 1995), and also silicates, resulting in the formation of soluble manganese fluorides and silicates. The high solubility of manganese fluorides implies that there can be an immediate uptake of manganese ions in the respiratory tract, including the nasal/head airways, the tracheobronchial region, and the alveolar or pulmonary region. If potassium is present in the welding fume, potassium permanganate might also be formed and potentially be dissolved in the respiratory tract.

The solubility of manganese (oxides) from welding fume is strongly affected both by pH and the content of ligands in the media used, as indicated from solubility studies in GMB and HS (Berlinger et al., 2008). The effect of acidity might be seen comparing manganese solubility in media with different acidity, but with otherwise similar properties (i.e. no strong binding ligands), such as PBS, NH_4Ac, water, and also Gamble's solution. The result indicates that the solubility of manganese from arc welding fumes in general is considerably lower above pH 7 than at pH 5 and lower. The effect on solubility due to complexation with ligands in the media might be discerned if the solubility in HS is compared with the solubility in each of the other media, given the same pH, extraction time, and temperature. At pH 7.4, the manganese solubility for GMAW-SS in HS is 14% (extraction time 24 h). In the other media, manganese solubility is maximum 1.1% at pH 7.4 (extraction time 24 h). On the other hand, the solubility of manganese from SMAW-SS fume does not seem to be higher in HS than that in the other media. Thus, the dissolved amount of manganese relative the total amount in the fume (which varies greatly depending on welding technique, welding material, and consumables) tends to be larger in SMAW fumes than in GMAW fumes, except in protein-rich media, such as HS. Presumably, this finding is due to the high water solubility of SMAW fumes. Because SMAW have been found to generate more fume than GMAW (Wallace et al., 2010), the absolute concentration of soluble manganese are likely to be higher in SMAW fumes.

The tendency of smaller particles to agglomerate in a given medium (thereby affecting manganese solubility) depends on parameters such as the media composition, i.e. pH, ionic strength, organic content, and also on particle concentration (Jenkins et al., 2005b; He et al., 2008, Murdock et al., 2008). For example, in a study by Schulze et al. (2008) on

agglomeration effects in the presence of serum proteins, a concentration of only 5% of serum in cell medium resulted in a reduced size of agglomerates for different metal oxide particles. It is believed that serum proteins adsorb onto the particle surfaces, thereby constituting a steric stabilization that prevents the particles from coming close to one another and form agglomerates (Bihari et al., 2008). It is likely that a low degree of agglomeration in one media might increase the amount of dissolved manganese in that media. This implies that it is important to characterize any collected welding fume used in solubility experiments, with respect to particle sizes and degree of agglomeration. As discussed in the Particle Formation section, particle sizes and degree of agglomeration vary greatly depending on the distance from the arc, i.e. the number concentration decreases with distance from the welding nozzle, and the number concentration for the smaller particles decreases substantially when residence time is increased because they are scavenged by larger ones through coagulation (Zimmer and Biswas, 2001). Thus, the fume sample distance from the source affects the size distribution of particles and thereby plays a role for the solubility of the collected fume and possibly also for its toxicity.

As discussed, the solubility of a particular welding fume will depend to a large extent on the media. Because the composition of the media is of great importance for the manganese speciation in that media, the media will be crucial for the speciation and possible transport routes of manganese in vivo. Studies indicate that trivalent manganese is transported in human plasma along with iron bound to Tf (Aschner and Aschner, 1990). Tf binds a variety of metal ions and is important in several areas of biochemistry and pharmacology. The transferrins all possess two specific metal-binding sites, and all have a high binding affinity for the Fe^{3+} ion. However, under normal conditions, serum Tf is only approximately 30% saturated with iron (Harris et al., 1994), leaving a high binding capacity for other metal ions. Thus, there is considerable evidence that Tf is a natural carrier for manganese. Moreover, studies have suggested that chronic exposure to manganese might be associated with altered iron concentrations in blood and in cerebrospinal fluid, which might be due to manganese–iron interaction at certain iron–sulfur-containing proteins, which regulate iron homeostasis. These findings have been suggested to be associated with the neurotoxicity of manganese (Chen et al., 2001; Zheng et al., 1998, 1999; Zheng and Zhao, 2001; Zheng, 2001). Gunshin et al. (1997) noted that divalent manganese (as well as divalent

iron) was transported by the divalent metal transporter 1 (DMT-1), and these mechanisms were further investigated by Mims and Prchal (2005) and Au et al. (2008). Crithfield et al. (2002) suggested that Mn^{2+} undergoes oxidation to Mn^{3+} before its association with Tf. The fact that Mn^{3+} more rapidly associates with Tf to form a stable complex was also found by Harris et al. (1994) and has later been verified by Reany et al. (2002). On the basis of these findings, future focus should be set on solubility in media that mimics fluids in various parts of airways as closely as possible and media that mimics the conditions in which manganese are proposed to be transported in to the cell, i.e. containing transport proteins that have been found to interact with divalent manganese (such as DMT-1) and trivalent manganese (such as Tf). Animal studies show that manganese absorbed in the divalent form from the gut via the portal blood, and thereby complexed with plasma proteins, is efficiently removed by the liver, whereas Tf-bound trivalent manganese is not as readily removed by the liver (Andersen et al., 1999). Still, future solubility studies on manganese welding particles in human gastric juice is needed to investigate the fractions of divalent (and possibly trivalent/tetravalent) manganese that actually can be dissolved from such particles under prevailing conditions. In addition, equilibrium studies on the complexation of competing metal ions, such as cobalt and iron (sharing the same GI transportation system), with plasma proteins are important to clarify the destiny of manganese ions in the presence of iron and cobalt.

The most common route for manganese (as well as iron) to the brain are via the blood–brain barrier, but manganese can bypass the blood–brain barrier and enter the brain directly via olfactory transport (Tjalve and Henriksson. 1999). Although the majority of inhaled welding particles are expected to deposit in the alveolar or pulmonary region, due to solubility properties and size fractions, a significant number of particles might deposit in the nasal/head airway region. Preferably, a large number of these particles can be expected to be more soluble than the oxides, i.e. particles containing fluorides or silicates of manganese, thus being more easily available to the body, e.g. by complexation with proteins in saliva and/or other GI proteins (Amico et al., 1979), by complexation with carnosine (β-alanyl-L-histidine), or by complexation with proteins at the surface of epithelial cells in the airways. If welding particles that deposit in the nasal/head airway region can bypass the blood–brain barrier and enter the brain directly via olfactory transport, equilibrium and solubility studies of such particles

or complexes are important. At present, solubility studies that mimic the conditions for human olfactory transport is lacking, and the importance of this system in contributing to the overall human neurotoxicity of manganese via inhalation is not known (Antonini et al., 2006b).

Well-defined equilibrium studies on particles derived from welding are necessary to understand and predict the in vivo solubility of manganese (as well as other metal ions in welding particles) as a function of pH and media composition. In addition, the research on in vitro solubility of manganese containing welding fumes could perhaps benefit more than today from the research on manganese homeostasis, i.e. on regulation and transportation of manganese in the human body. Additional studies on manganese protein interactions and the close relationship between manganese homeostasis and iron homeostasis can be found in the review by Fitsanakis et al. (2010).

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