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Inhalation exposure of gas-metal arc stainless steel welding fume increased atherosclerotic lesions in apolipoprotein E knockout mice☆

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ABSTRACT

Epidemiological studies suggest that welding, a process which generates an aerosol of inhalable gases and metal rich particulates, increases the risk for cardiovascular disease. In this study we analyzed systemic inflammation and atherosclerotic lesions following gas metal arc-stainless steel (GMA-SS) welding fume exposure. Apolipoprotein E knockout (apoE$^{-/-}$) mice, fed a Western diet, were exposed to GMA-SS at 40 mg/m^3 for 3 h/day for ten days (~8.26 μg daily alveolar deposition). Mice were sacrificed two weeks after exposure and serum chemistry, serum protein profiling and aortic lesion area were determined. There were no significant changes in serum total cholesterol, triglycerides or alanine aminotransferase. Serum levels of uric acid, a potent antioxidant, were decreased perhaps suggesting a reduced capacity to combat systemic oxidative stress. Inflammatory serum proteins interleukin 1 beta (IL-1β) and monocyte chemoattractant protein 3 (MCP-3) were increased two weeks after GMA-SS exposure. Analysis of atherosclerotic plaques showed an increase in lesion area as the result of GMA-SS exposure. In conclusion, GMA-SS exposure showed evidence of systemic inflammation and increased plaque progression in apoE$^{-/-}$ mice. These results complement epidemiological and functional human studies that suggest welding may result in adverse cardiovascular effects.

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1. Introduction

Recent epidemiological studies suggest a link between a pulmonary exposure to particulate matter (PM) air pollution and an adverse cardiovascular outcome (Brook et al., 2010). In both human and animal studies, PM exposure has been shown to increase the progression of atherosclerosis (reviewed in Brook et al., 2010). Welding represents a unique PM exposure because of the generation of an inhalable fume along with metal particulates that have varying solubility (Antonini, 2003). Therefore, welders, an understudied workforce consisting of an estimated 5 million part-time worldwide with approximately 412,000 fulltime workers in the United States (Bureau of Labor Statistics), represent an at-risk population with the potential for cardiovascular effects. A higher risk for cardiovascular disease has been shown in several epidemiological studies related to welding (Hilt et al., 1999; Ibfelt et al., 2010; Moulin et al., 1993; Newhouse et al., 1985; Sjogren et al., 2002; Suadicani et al., 2002). Multiple recent studies of welders have suggested potential mechanisms related to cardiovascular disease. Changes in cardiovascular parameters in welders include effects on heart rate variability, aortic augmentation index (a surrogate marker of arterial stiffness) and markers of systemic inflammation and oxidative stress (Cavallari et al., 2008; du Plessis et al., 2010; Fang et al., 2008, 2009; Han et al., 2005; Kim et al., 2005; Li et al., 2004; Magari et al., 2001).

To date, addressing potential systemic effects of welding, specifically related to cardiovascular disease, in animal inhalation studies are absent. Animal studies offer a unique ability to study the effects of a single exposure without confounders such as lifestyle and additional environmental and workplace exposures of human welders. This study addressed systemic inflammation and atherosclerotic

Abbreviations: GMA-SS, gas metal arc-stainless steel; apoE$^{-/-}$, apolipoprotein E knockout mice; IL-1β (*Il1b*), interleukin 1 beta; CCL7 (*Ccl7*), chemokine (C–C motif) ligand 7; MCP-3, monocyte chemoattractant protein 3; *Il6*, interleukin 6; *Cxcl2*, chemokine (C–X–C motif) ligand 2; *Ccl2*, chemokine (C–C motif) ligand 2; CCR2, chemokine (C–C motif) receptor 2; PM, particulate matter; TLV, threshold limit value; PEL, permissible exposures limit; Cr^{IV}, hexavalent chromium; SA, alveolar epithelial surface area; CNT, carbon nanotubes.

☆ The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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Table 1
Pulmonary deposition of GMA-SS welding fume.

	AIR ($n=7$) (μg/sample)	GMA-SS ($n=7$) (μg/sample)	Deposition (wt%)	Fume (wt%)
Cr	0.215 ± 0.002	2.307 ± 0.106	17.7	20.2
Cu	0.353 ± 0.009	0.450 ± 0.011	0.8	0.2
Fe	13.929 ± 0.792	20.614 ± 0.779	56.6	57.0
Mn	0.030 ± 0.002	2.153 ± 0.087	18.0	13.8
Ni	0.016 ± 0.001	0.825 ± 0.033	6.9	8.8

lesion area in apoE$^{-/-}$ knockout mice exposed to gas metal arc-stainless steel (GMA-SS) welding fume.

2. Methods

2.1. Animals and exposure conditions

C57BL/6 and apoE$^{-/-}$ (B6.129P2-Apoe^{tm1Unc}) mice from Jackson Laboratory (Bar Harbor, ME) were used in this study. All mice were provided food (Teklad 7913 unless otherwise specified) and tap water *ad libitum* in ventilated cages in a controlled humidity and temperature environment with a 12 h light/dark cycle. Animal care and use procedures were conducted in accordance with the "PHS Policy on Human Care and Use of Laboratory Animals" and the "Guide for the Care and Use of Laboratory Animals" (NIH publication 86-23, 1996). These procedures were approved by the National Institute for Occupational Safety and Health Institutional Animal Care and Use Committee.

Mice were exposed by inhalation to GMA-SS welding fume at a concentration of 40 mg/m^3. The welding fume generation system and characterization for this particular fume have been extensively described (Antonini et al., 2006, 2007). Levels of ozone and carbon monoxide were monitored to not exceed previously published values. Low amounts of ozone were formed in the chamber during the exposure period but not significantly higher than background levels (Antonini et al., 2006, 2007). The levels of ozone were lower than the NAAQS criteria of 75 ppb. Carbon monoxide levels were not significantly higher than background levels (Antonini et al., 2006, 2007).

2.2. Pulmonary deposition of GMA-SS

Preliminary experiments were performed to assess pulmonary metal deposition in C57BL/6 mice, the background strain of the apoE$^{-/-}$ mice ($n=7$ air and $n=7$ GMA-SS). Mice were exposed to 40 mg/m^3 GMA-SS for 3 h, immediately sacrificed and whole lungs were harvested. The tissue was digested and total metal content was determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES) according to NIOSH method 7300 modified for microwave digestion (REF NIOSH, 1994).

2.3. Exposure design for apoE$^{-/-}$ mice

Atherosclerotic prone apoE$^{-/-}$ mice aged 10 weeks were fed the Western diet (Harlan TD88137). After five weeks on the diet, mice were randomized and exposed to either air ($n=9$) or GMA-SS ($n=9$) at 40 mg/m^3 for 3 h/day for five days a week for two weeks and then tissues were harvested two weeks after the final exposure. The serum was collected for chemistry (AniLytics, MD) and multi-analyte profiling by RodentMAP v1.6 (Rules Based Medicine, TX). The lung was harvested for gene expression by real-time RT-PCR as previously described (Erdely et al., 2009). Lung samples were isolated using the RNeasy Mini Kit (Qiagen, CA). Evaluation of gene expression was determined by standard 96-well technology using the StepOne™ with pre-designed Assays-on-Demand™ TaqMan® probes and primers (Applied Biosystems, CA). Probe and primer assays included *Il6* (Mm99999064_m1), *Ccl2* (Mm99999056_m1), *Cxcl2* (Mm00436450_m1), *Ccl7* (Mm00443113_m1) and *Il1b* (Mm01336189_m1).

2.4. Measurement of atherosclerotic plaques

The aorta was evaluated for plaque development by the following method. Unstained aortas were displayed en face and images were taken. The grayscale image of the aorta (the arch with a consistent length of thoracic segment) was inverted thereby converting the plaques from white to black. Images were then uploaded into Image Quant 5.2 software. An area was determined for each plaque and the sum of all plaque areas was divided by the total area of the aorta. Also, a given plaque intensity and an equal sized background from an adjacent non plaque area in the vessel was determined. The sum of plaque intensity subtracted from the corresponding background intensity was factored for total aorta area. The above methodology was subsequently confirmed by blinded analysis by a different individual by the more traditional method of plaque staining by Oil-Red O (Branen et al., 2001). At room temperature, the aortas were prepared for staining by incubating in 78% methanol for 1 min. This was followed by a 40 min incubation in freshly prepared 0.2% Oil Red O (in 78% MeOH and 0.2 M NaOH). Destaining was performed using 78% methanol once for 5 min and twice for 2 min. Distilled water was used as a final wash, 2 times for 2 min.

2.5. Statistics

All data are presented as means ± standard error. Analysis of effects in this study was between two groups; therefore, data were compared by Student's *t*-test. Differences were considered statistically significant at $p<0.05$.

3. Results

3.1. Welding fume characteristics and pulmonary deposition

The summary of the components of the GMA-SS fume is given in Table 1. The fume consists primarily of iron, chromium, manganese, nickel and copper with trace amounts of silicon, aluminum and vanadium. The solubility of the metals in this particular fume is relatively low. The calculated mass median aerodynamic diameter of the GMA-SS fume was 0.255 μm indicating a high probability of alveolar deposition (Antonini et al., 2007). To determine the actual metal deposition following welding fume exposure, mice were exposed to GMA-SS at a PM mass concentration of 40 mg/m^3 for 3 h. Immediately following exposure, lungs were harvested and metal composition was analyzed. The deposition of metals (Table 1) illustrates a cumulative increase of 11.8 μg of total welding fume deposited in the lung from a single exposure. The metal analysis by weight % of the whole lungs agrees relatively well with the weight % of collected fume suggesting that the fume is inhaled into the lung uniformly. The alveolar deposition of the welding fume was estimated at 70% from the total lung deposition (Raabe et al., 1988) suggesting ~8.26 μg alveolar deposition. The alveolar deposition in the mice was equated to the human by the equations below referencing the previous TLV of 5 mg/m^3 for total welding fume and the PEL of 5 μg/m^3 for Cr^{VI}.

Factored for human dose using previous TLV of 5 mg/m^3:

$$\text{Fume concentration} \times \text{min volume} \times \text{exposure duration} \times \text{deposition efficiency} = \text{deposited human dose}$$

$$5\ \text{mg/m}^3 \times (20\ \text{L/min}) \quad (10^{-3}\ \text{m}^3/\text{L}) \times (8\ \text{h/day}) \quad (60\ \text{min/h}) \times 0.16 = 7.7\ \text{mg deposited per 8 h day in humans}$$

Human equivalent dose to mouse by body weight:

$$(\text{Weight}_{\text{human}} \times \text{Deposition}_{\text{mouse}})/\text{Weight}_{\text{mouse}} = \text{Deposition}_{\text{human}}$$

$$(75\ \text{kg} \times 0.00826\ \text{mg})/0.025\ \text{kg} = 24.8\ \text{mg equivalent human deposition}$$

Human equivalent dose to mouse by SA (Stone et al., 1992):

$$(\text{SA}_{\text{human}} \times \text{Deposition}_{\text{mouse}})/\text{SA}_{\text{mouse}} = \text{Deposition}_{\text{human}}$$

$$(102\ \text{m}^2 \times 0.00826\ \text{mg})/0.05\ \text{m}^2 = 16.9\ \text{mg}$$

Factored for human dose using Cr^{VI} PEL of 5 μg/m^3:

$$\text{Cr}^{VI}\ \text{concentration} \times \text{min volume} \times \text{exposure duration} \times \text{deposition efficiency} = \text{deposited human dose}$$

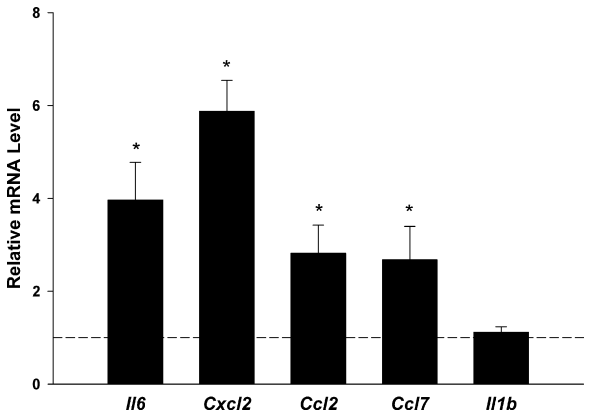

Fig. 1. Effect of GMA-SS on pulmonary inflammatory gene expression. Lungs from GMA-SS exposed (black bars) were compared to air exposed apoE$^{-/-}$ mice (arbitrarily set at 1.0 indicated by dotted line). Abbreviations include interleukin 6 (*Il6*), chemokine (C–X–C motif) ligand 2 (*Cxcl2*; also known as macrophage inflammatory protein 2), chemokine (C–C motif) ligand 2 (*Ccl2*; also known as monocyte chemotactic protein 1), chemokine (C–C motif) ligand 7 (*Ccl7*; also known as monocyte chemotactic protein 3) and interleukin 1 beta (*Il1b*). *$p < 0.05$ vs air.

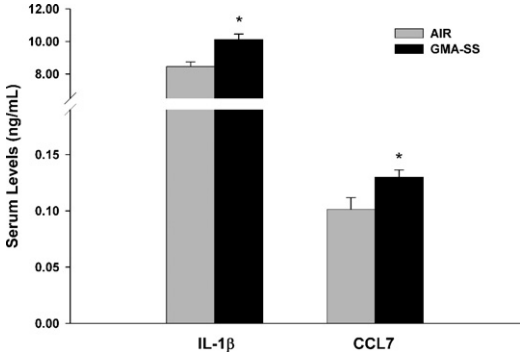

Fig. 2. Effect of GMA-SS on serum inflammatory proteins. Abbreviations include interleukin 1 beta (IL-1β) and chemokine (C–C motif) ligand 7 (*Ccl7*; also known as monocyte chemotactic protein 3). *$p < 0.05$ vs air.

$5\ \mu g/m^3 \times (20\ L/min) \quad (10^{-3}\ m^3/L) \times (8\ h/day) \quad (60\ min/h) \times 0.16 = 7.7\ \mu g$ deposited per 8 h day in humans

In the GMA-SS fume, Cr^{VI} totaled 2600 μg/g or 0.26% of the total welding fume (Keane et al., 2009). Using our alveolar deposition dose of 8.26 μg roughly 0.0215 μg would be Cr^{VI}.

Human equivalent dose to mouse by body weight:

$$(Weight_{human} \times Deposition_{mouse})/Weight_{mouse} = Deposition_{human}$$
$$(75\ kg \times 0.0215\ \mu g)/0.025\ kg = 64.5\ \mu g \text{ equivalent human deposition}$$

Human equivalent dose to mouse by SA:

$$(SA_{human} \times Deposition_{mouse})/SA_{mouse} = Deposition_{human}$$
$$(102\ m^2 \times 0.0215\ \mu g)/0.05\ m^2 = 43.9\ \mu g$$

Therefore, our welding fume dose in the mouse is equivalent to approximately 2–3.5 times greater than the TLV of 5 mg/m^3 for total welding fume. The dose in comparison to the PEL for Cr^{VI} of 5 μg/m^3 would be approximately 5.5–8.5 times greater.

Table 2
Effects of GMA-SS inhalation exposure on serum chemistry measurements.

	AIR	GMA-SS
Cholesterol (mg/dL)	1157 ± 69	1012 ± 84
Triglycerides (mg/dL)	241 ± 19	264 ± 114
Alanine aminotransferase (U/L)	32 ± 3	40 ± 9
Lactase dehydrogenase (U/L)	204 ± 21	275 ± 27
Uric acid (mg/dL)	16 ± 2	9 ± 2*
Blood urea nitrogen (mg/dL)	27 ± 3	31 ± 3
Total protein (g/L)	7.5 ± 0.2	7.4 ± 0.4

* $p<0.02$

3.2. Pulmonary gene expression, serum chemistry and serum protein profiling

ApoE$^{-/-}$ mice were fed the Western diet for a total of 9 weeks with the ten days of exposure occurring during weeks 6 and 7. As expected, lung gene expression analysis showed a pulmonary inflammatory response that was still present two weeks after exposure (Fig. 1). Common genes of inflammation included *Il6*, *Cxcl2* and *Ccl2*. These genes were chosen as previous studies utilizing the same exposure conditions in C57BL/6 mice, the background strain of the apoE$^{-/-}$ mice, showed increased protein levels in the bronchoalveolar lavage fluid (Zeidler-Erdely et al., 2011a). Serum Chemistry measurement for apoE$^{-/-}$ exposed to air or GMA-SS welding fume is shown in Table 2. There were no alterations in circulating cholesterol levels, triglycerides, alanine animotransferase, total protein or blood urea nitrogen. There was a trend for increased lactate dehydrogenase and a significant decrease in uric acid levels (Table 2). Collected serum was analyzed for 69 analytes by multiplex technology. IL-1β and CCL7 (also known as MCP-3) were found to be increased two weeks after welding fume exposure had ended (Fig. 2). Gene expression was increased in lungs for *Ccl7* but not

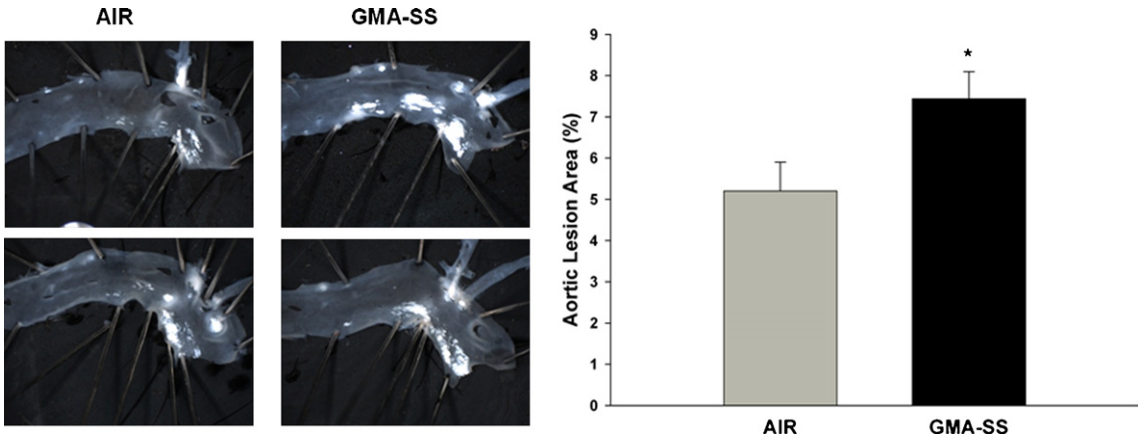

Fig. 3. Effect of GMA-SS atherosclerosis progression. Representative images of unstained aortas for air and GMA-SS exposed mice are shown on the left with total lesion area (%) shown on the right. *$p < 0.05$ vs air.

Il1b (Fig. 1). Acute phase proteins including C-reactive protein, haptoglobin and serum amyloid P were not altered in the serum at this time point (data not shown).

3.3. Analysis of atherosclerotic plaque lesions

The aorta was harvested from apoE$^{-/-}$ mice and analyzed for plaque content by the en face method. Under the specific conditions of unstained plaques and inverted images, thereby making the plaques black and utilizing standard Western blot software analysis, there was increased lesion area (%) in the aortas of GMA-SS exposed mice (Fig. 3). In addition, the plaques were stained with Oil Red O and quanitification also showed a significant increase in plaque area (0.64 ± 0.15 air vs 1.70 ± 0.28* GMA-SS, $^*p < 0.01$). The use of traditionally stained plaques verifies our methodology and result of analyzing unstained inverted images. Also, plaque intensity determined by our method was increased in the GMA-SS exposed mice (6.6 ± 1.0 air vs 10.3 ± 1.2* GMA-SS, $^*p < 0.05$).

4. Discussion

Epidemiological and acute human studies have shown adverse cardiovascular effects among welders. Therefore, occupational exposure to welding fume can be recognized as a cardiovascular disease risk factor. Given the known association with PM air pollution and cardiovascular disease (Brook et al., 2010), the effects in welders may not be surprising given the fact that welders can be exposed to much higher levels of PM than the general public. The main contribution of this study was increased progression of atherosclerosis following inhalation to GMA-SS welding fume. This study, the first animal inhalation study to explore cardiovascular effects of welding fume, provides experimental evidence to support epidemiological findings. Furthermore, the utility of controlled animal studies allows for the evaluation of welding fume exposure absent of confounding factors. These factors, including multiple exposures (i.e., asbestos, silica) and job duties other than welding (i.e., soldering, grinding) combined with lifestyle (i.e., alcohol, smoking, diet), make the effects specific to welding fume in humans difficult to assess.

The 5 mg/m^3 TLV for total welding fume was previously withdrawn. The new PEL will regulate welding fume based on the most toxic containing metal. For the stainless steel welding fume used in this study, Cr^{VI} will determine the exposure limit, which is currently 5 μg/m^3. Using the old standard of 5 mg/m^3 for total welding fume, our daily exposure was approximately 2–3.5 times (or 4–7 weeks total) that of a welder working at the maximum exposure limit for 8 h. In reference to the Cr^{VI} content, our exposure was 5.5–8.5 times (or 11–17 weeks total) the current level recommended for exposure. It has been documented that welders can experience significantly greater than permissible exposure limits at the breathing zone and welding is sometimes performed in areas with poor ventilation (Korczynski, 2000; Susi et al., 2000). Therefore, our deposition dose in the mouse is a very reasonable approximation of a human exposure.

Many different pulmonary exposures including air pollution (both PM and non-particulate contaminants), single walled carbon nanotubes and high dose carbon black have shown increased progression of atherosclerosis and/or vulnerability of atherosclerotic plaques (Brook and Rajagopalan, 2010; Brook et al., 2010; Campen et al., 2010; Li et al., 2007; Niwa et al., 2007; Sun et al., 2005). Since atherosclerosis is well established as an inflammatory disease (Libby et al., 2009), one of the potential mechanisms by which a pulmonary exposure can promote atherosclerosis is spill-over of the lung inflammatory response (Brook and Rajagopalan, 2010). In support, the above mentioned pulmonary exposures that increased atherosclerosis progression also induce systemic inflammation. Specifically, exposure to carbon nanotubes (CNT), which increased lesion area (Li et al., 2007), resulted in a systemic inflammatory response that reflected the ongoing pulmonary response (Erdely et al., 2009). In this study, serum levels of IL-1β and CCL7 were increased indicating the occurrence of systemic inflammation. Previous studies indicated *Ccl7* and *Il1b* were mediators of GMA-SS-induced pulmonary inflammation (Erdely et al., 2010; Zeidler-Erdely et al., 2011b), supported by increased *Ccl7* in this study, providing the potential for spill-over into the periphery. IL-1β is a proinflammatory cytokine involved in atherosclerosis as lack of IL-1β decreased atherosclerotic lesion size in apoE$^{-/-}$ mice (Kirii et al., 2003). CCL7, a cytokine which attracts and activates various leukocytes (Menten et al., 2001), may also be linked to atherosclerosis progression. CCL7 can interact with the CCR2 receptor, and studies have clearly shown the beneficial effects of CCR2 knockout and atherosclerosis progression (Boring et al., 1998; Dawson et al., 1999). Also, reduced plaque progression in the apoE$^{-/-}$ mice has been associated with reduced plasma CCL7 levels (Cuaz-Perolin et al., 2008).

Sampling for serum inflammatory proteins can be difficult given the short half lives. Presumably, other inflammatory markers were increased during the two weeks of and/or in the two weeks after exposure that we did not detect by only measuring at a single time point. Mediators of systemic inflammation are currently being measured at earlier time points after welding fume exposure in ongoing studies. Previously, we have shown that following CNT exposure primary inflammatory mediators were increased rapidly giving way to an acute phase response but the effects were transient (Erdely et al., 2009; Hulderman et al., 2011). Welding fume, in particular the GMA-SS fume used in this study, is a well described exposure resulting in pulmonary inflammation, oxidative stress and injury (Antonini, 2003; Antonini et al., 2007; Zeidler-Erdely et al., 2011a; Zeidler-Erdely et al., 2010) strongly suggesting the potential for the systemic translocation of pulmonary inflammation. Previous studies in human welders have shown systemic inflammation and oxidative stress as well as impaired vascular and cardiac function as the result of welding exposure (Cavallari et al., 2008; du Plessis et al., 2010; Fang et al., 2009; Fang et al., 2008; Han et al., 2005; Kim et al., 2005; Li et al., 2004; Magari et al., 2001). All of these factors can be linked to cardiovascular disease including advanced progression of atherosclerosis. The combined results of the human welding studies with correlation to other pulmonary exposures strongly support the findings of this study.

Measurements of cholesterol and triglycerides showed no effect due to GMA-SS exposure. This was not unexpected given our low dose exposure and previous studies of carbon nanotubes and PM exposure also had similar results (Li et al., 2007; Sun et al., 2005). Interestingly, serum levels of uric acid, a potent antioxidant formed from purine metabolism, were decreased in the GMA-SS exposed mice. A potential explanation for the reduced serum uric acid levels in GMA-SS exposed mice was redistribution, for example to the lung, as a protective measure as uric acid is consumed in the respiratory tract lining fluid following pollutant exposure (Behndig et al., 2006; Mudway et al., 1999; Romieu et al., 2008). One pollutant in particular, diesel exhaust, contains redox-active metals very similar to freshly generated welding fume (Antonini et al., 1998; Behndig et al., 2006). Furthermore, reduced plasma urate concentrations were associated with peripheral airway hyperreactivity (Freed et al., 1999) a condition described in welders (Hjortsberg et al., 1992). While the mechanism is unknown, the decreased serum uric acid suggests a reduced capacity to combat a systemic prooxidant state and possible small airway dysfunction in the exposed apoE$^{-/-}$ mice.

In conclusion, exposure to GMA-SS increased lesion development in atherosclerotic prone apoE$^{-/-}$ mice. These effects were accompanied by pulmonary inflammation and indications of systemic inflammation and oxidative stress. Our results provide complementary animal data to existing epidemiological evidence of increased risk of cardiovascular disease in welders.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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