This review examines whether exfoliated, virus-infected animal skin cells could be an important source of infectious foot and mouth disease virus (FMDV) aerosols. Infectious material rafting on skin cell aerosols is an established means of transmitting other diseases. The evidence for a similar mechanism for FMDV is: (i) FMDV is tropic for animal skin and FMDV epidermis titres are high, even in macroscopically normal skin; (ii) estimates for FMDV skin cell aerosol emissions appear consistent with measured aerosol emission rates and are orders of magnitude larger than the minimum infectious dose; (iii) the timing of infectious FMDV aerosol emissions is consistent with the timing of high FMDV skin concentrations; (iv) measured FMDV aerosol sizes are consistent with skin cell aerosols; and (v) FMDV stability in natural aerosols is consistent with that expected for skin cell aerosols. While these findings support the hypothesis, this review is insufficient, in and of itself, to prove the hypothesis and specific follow-on experiments are proposed. If this hypothesis is validated, (i) new FMDV detection, management and decontamination approaches could be developed and (ii) the relevance of skin cells to the spread of viral disease may need to be reassessed as skin cells may protect viruses against otherwise adverse environmental conditions.

Keywords: epidermal desquamation; virus excretion; aerosol emission; airborne transmission; epidemiology; foot and mouth disease

1. INTRODUCTION

Foot and mouth disease (FMD) is a highly contagious viral disease capable of causing widespread epidemics among livestock. It has a major economic impact when outbreaks occur in countries previously free from disease. The foot and mouth disease virus (FMDV) is virulent and has multiple known routes of transmission. These include direct contact (e.g. viral entry through mucous membranes, cuts or abrasions during animal-to-animal contact), indirect contact (e.g. fomites), ingestion (e.g. contaminated feed) and the respiratory or airborne pathway (e.g. the inhalation of infectious aerosols) [1]. The airborne pathway is suspected to play a key role in some outbreaks by causing disease ‘sparks’ (i.e. disease spread to regions remote from a primary infection site) [2,3]. If not detected in a timely fashion, such sparks can lead to major outbreaks. For example, the widespread dissemination of FMDV during the catastrophic 2001 UK outbreak was thought to be due to the inadvertent transport of animals with unrecognized FMDV infection from a Prestwick farm to areas previously free of FMDV [4].

Like other viral diseases with an airborne transmission pathway, the source of exhaled FMDV aerosols is generally considered to be virus exhaled from the respiratory system [1]. However, while whole-animal FMDV-infected aerosols have been extensively characterized, a literature search identified only one study [5] that directly demonstrated that the respiratory system was a source of airborne FMDV. It is also noteworthy that one study [6] measured significant emissions of infectious FMD aerosol when swine were placed in looseboxes after being killed—when, presumably, all respiratory release of virus had ceased.

This review examines the possibility that FMDV-infected skin cells may be an additional source of infectious FMD aerosols. Early researchers did previously raise the possibility that airborne FMDV-infected skin cells might be important in disease transmission [6–8]; however, this possibility was never systematically investigated. In contrast, respiratory mucosal epithelial cells are known to be a primary site of initial infection (pharynx), a main virus amplification site (mouth) and the site of persistent infection in carrier ruminants (pharynx) [1,9]. It is also known that FMDV is often found in oral–pharyngeal fluids containing cellular material while samples without cellular material are typically FMDV negative [1,9]. Collectively, these observations suggest that FMDV-infected, respiratory mucosal epithelial cells shed into respiratory fluids may contribute to respiratory emissions of FMDV aerosols. Mammalian skin actively sheds a significant number of skin cells (10⁶ to 10⁸ per day) into the environment [10–12] and skin cells have been observed to comprise a significant fraction (1–10%) of measured indoor and outdoor [9] aerosols and indoor dust [13–16]. Bacteria, yeast, fungi and viruses are present on the surface of skin cells (e.g. [17] and references within). When these skin cells mature and naturally exfoliate, the infectious material can become airborne (electronic supplementary material, Particle Suspension Mechanisms), travel to new hosts and cause infection when inhaled or deposited directly onto the skin of the...
new host [10,18–22]. This mechanism is believed to be a significant source of bacterial infection for surgical procedures and other nosocomial infections [10,18]. Transmission of viral disease via the inhalation of infectious skin cells is less well studied, but may be documented in at least one case (electronic supplementary material, Other Viral Diseases).

The purpose of the current study is to systematically review published data relevant to the hypothesis that skin cells could be a source of infectious FMDV aerosols. Estimates are provided for (i) skin cell shedding rates, (ii) FMDV skin concentrations and (iii) the shedding rate of FMDV-infected skin cells. In addition, the expected characteristics of an infectious FMDV skin cell aerosol source are placed in context with known experimental data. These include measurements of whole-animal FMDV aerosol emissions in relation to timing, aerosol stability, aerosol size and magnitude. Suggestions for future experiments are provided.

2. ESTIMATING THE SHEDDING RATE OF FOOT AND MOUTH DISEASE VIRUS-INFECTED SKIN CELLS

(a) Animal skin cell shedding rate

As part of the normal skin growth cycle, mammalian skin cells normally move progressively from basal cells (stratum basale) within the epidermal layer of the skin outward to the stratum corneum, where old skin cells then exfoliate into the environment. In adult humans (the most studied species with respect to airborne skin cell emissions), healthy skin typically sheds one cell layer per day. Exfoliated skin cells are typically shed as individual hexagonal plates, 25 μm on a side and 0.1–0.5 μm thick [11,12]. Mature skin cells (corneocytes) can become airborne by air moving across the skin surface [23] (see also electronic supplementary material, Particle Suspension Mechanisms); however, emissions over a short period of time can significantly increase with mechanical abrasion (e.g. rubbing of clothes or body parts [24]), physical activity [25,26] and/or washing [27]. Exfoliated skin cells in settled dust may become re-aerosolized by human (animal) activity [13,20,21] (see also electronic supplementary material, Particle Suspension Mechanisms). The median aerodynamic diameter of human skin cells is approximately 14 μm. In fresh [25,28] and environmentally processed [16] emissions, skin cells are observed at both smaller and larger sizes—although the size distribution of aerosols derived from skin cells is not precisely defined in the current literature.

Human skin bears many similarities to the skin of domestic animals that have been documented to emit airborne FMDV (e.g. swine, cattle and sheep) [29–34]. The similarities include general structure, skin cell size and epidermal cell turnover time. Based on these similarities, swine, cattle and sheep can be expected to normally shed one layer of skin cells per day. Considering an animal’s skin surface area, a nominal epidermis thickness of 100 μm and an assumed skin density of 1 g cm$^{-3}$, the estimated mass of epidermal material shed per day is 2 g for swine and sheep and 10 g for cattle.5

(b) Animal skin foot and mouth disease virus concentrations

While not a typical site for the initial FMDV infection, the skin is a major viral replication site in most animals studied [1,8,35–39]. Table 1 and electronic supplementary material, table S1 summarize the available literature on FMDV skin concentrations. FMDV skin concentrations (§2a,b) are estimated by multiplying the skin cell shedding rate by the peak FMDV skin concentrations (§2a,b). This calculation yields a peak FMDV skin concentration (by several orders of magnitude) within the epidermis [37,39]. In situ hybridization and immunofluorescence studies indicate that the initial FMDV replication site is located in the deeper basal layers of the epidermis (basal cells proper or the stratum spinosum layer just above) and that FMDV-laden cells migrate outward towards the skin surface. There is no evidence of active virus replication in the stratum corneum [37,42,45,46]. Brown et al. [37,46] reported FMDV present within the cell cytoplasm of all epidermal skin layers in macroscopically normal epidermis. Other studies [45,46] have not observed the FMDV signal in the intact, non-lesional stratum corneum. There are no known studies of the infectivity of the stratum corneum in animal skin.

(c) Peak foot and mouth disease virus-infected skin cell shedding rates

The peak FMDV skin cell shedding rate is estimated by multiplying the skin cell shedding rate by the peak FMDV skin concentrations (§2a,b). This calculation yields a peak FMDV skin cell shedding rate of approximately 10$^6$ TCID$_{50}$ per animal per day for swine and cattle, respectively, based on non-lesional FMDV skin concentration measurements. This estimate is approximate and does not include the contributions of infected FMDV skin cells derived from lesional material—which contains FMDV concentration orders of magnitude higher than non-lesional skin. It also does not include the contribution of skin externally contaminated with infectious FMDV. Both of these mechanisms would be expected to increase the net infectious skin cell shedding rate. The fraction of shed skin cells that are aerosolized, either initially or at a later time, is likewise unknown, but the FMDV-infected skin cell aerosol emission rate would be less than the skin cell shed rate estimated in this...
This estimate does not assume that all shed skin cells contain the same amount of infectious FMDV. For perspective, it is informative to note that a recent review of the FMD infectious dose via the aerosol route suggested that the minimum FMD infectious dose is 11 TCID$_{50}$ for sheep, 25 TCID$_{50}$ for cattle and 180 TCID$_{50}$ for swine [47]. The estimated peak FMDV skin cell emission rate of approximately $10^6$ TCID$_{50}$ per animal per day for swine and cattle exceeds these figures by orders of magnitude, and so, in theory, FMDV could be transmitted via an infected skin cell pathway. This daily FMD excretion rate from exfoliated skin cells is approximately the same magnitude as that estimated to be due to urine or faeces [1]. It is also about 10 to 100 times greater than the FMD aerosol emissions measured directly from infected swine respiratory systems [5]. There are, however, important unknowns in the latter comparison. For example, the latter study did not account for aerosol losses and so probably underestimated the total respiratory emissions.

### 3. PROVIDING CONTEXT TO THE HYPOTHEZIZED FOOT AND MOUTH DISEASE SKIN AEROSOL SOURCE

#### (a) Timing of foot and mouth disease virus aerosol emissions

The timing of FMDV emergence in skin tissue is consistent with the skin being a source of infectious aerosols. In swine (but less clearly in cattle and sheep), emissions of airborne virus are observed to begin (and peak) coincident with the onset of clinical signs of FMD (e.g. the development of visible lesions outside the inoculation site)—the time when FMDV skin concentrations peak. Emissions then persist for several days [1,5,7,48,49]. While this may generally be the case, airborne FMD has occasionally been observed to begin on the day before clinical signs appear or alternatively to begin as much as several days after the development of clinically evident lesions. However, a general association of FMDV aerosol emissions with clinical skin lesion development is particularly strong in the swine experiments in which infection occurred via airborne or direct contact [50]. In these experiments, most animals emitted no airborne virus prior to skin lesion development and no airborne emissions were reported more than 1 day prior to the development of the clinical signs of FMD [5,7,50].

#### (b) Whole-animal foot and mouth disease virus aerosol emission rates

While FMD was first proved to be capable of airborne spread in the 1930s [51], it was not until the 1960s that detailed experiments were first performed to characterize the emission of infectious FMD aerosols. Many of the published laboratory studies of FMD aerosol emissions were performed at the UK Institute of Animal Health and have been performed using similar experimental conditions. While it is beyond the scope of this study to provide a detailed review of the kinetics and magnitude of FMD aerosol emissions, table 2 and electronic supplementary material, table S2 provide a summary of published estimates of the peak whole-animal FMD aerosol emission rate (i.e. the average emission rate per animal per 24 h period [4] for the day of maximum emissions). The total amount of FMDV collected by the air sampler was converted into a 24 h emission rate using equation

### Table 1. Peak external skin FMDV concentrations. AVE, average of values.

<table>
<thead>
<tr>
<th>Sample location</th>
<th>Average FMDV skin concentration (log$<em>{10}$(TCID$</em>{50}$/g))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremity</td>
<td></td>
</tr>
<tr>
<td>Lesion</td>
<td>[40] 4.9</td>
</tr>
<tr>
<td>No lesion</td>
<td>[43] 4.7</td>
</tr>
<tr>
<td>Non-extremity</td>
<td></td>
</tr>
<tr>
<td>Ave</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Units reported are TCID$_{50}$—the amount of virus required to infect 50% of all thyroid tissue (BTY) cultures [44]. Measurements reported using methods other than BTY cultures have been scaled. Measurements reported below the instrument detection limits are assumed to be 0 for calculation purposes. See electronic supplementary material, table S1, for details.

Scaled from lesion results based on data reported in Monaghan et al. [42].
(3.1) and airborne FMDV concentrations either directly reported or calculated from equation (3.2). Equation (3.1) was derived assuming a steady-state air concentration (i.e., losses within the animal-holding area are balanced by animal emissions), well-mixed air (i.e., air concentrations are the same at all locations within the loosebox) and a 4$\times$3$\times$3 m ($3.6 \times 10^4$ l) loosebox.

$$FMDV_{\text{emissions}} = \frac{[FMDV]_{\text{air}} \times V_{\text{loosebox}} \times (L_{\text{aerosol}} + L_{\text{ACH}})}{N_i},$$

(3.1)

where $FMDV_{\text{emissions}}$ is the FMDV aerosol emission rate in TCID$_{50}$ per animal per day, $[FMDV]_{\text{air}}$ is the measured FMDV air concentration in TCID$_{50}$ per litre, $V_{\text{loosebox}}$ is the loosebox volume, $L_{\text{aerosol}}$ is the measured loosebox FMDV aerosol loss rate with no air exchange (144 per day) (§3c), $L_{\text{ACH}}$ is the air exchange rate during the sampling period and $N_i$ is the number of infected (FMDV excreting) animals in the loosebox.

$$[FMDV]_{\text{air}} = \frac{\text{total FMDV collected}}{\text{air flow rate} \times t_{\text{sampling}}},$$

(3.2)

where total FMDV collected is the total amount of FMDV in the liquid sampling media in TCID$_{50}$, air flow rate is the sampling instrument air flow rate in litres per minute and $t_{\text{sampling}}$ is the sampling duration in minutes.

Overall, the average per animal peak FMDV aerosol emission rate is estimated to be approximately $10^7$ TCID$_{50}$ per day for swine and $10^{4.5}$ TCID$_{50}$ per day for cattle and sheep. These whole-animal emission values are similar in magnitude to the infected skin cell shedding rate of $10^6$ TCID$_{50}$ per day previously estimated for swine and cattle. One study compared whole-animal (swine) infectious aerosol emission rates from live and dead animals, and reported that FMDV aerosol concentrations (and thus emission rates) decreased by 10–100-fold when animals were slaughtered [6]. The dead swine FMDV aerosol emission rate was similar to that reported above for (live) sheep and cattle, and is 10 per cent of the total infected FMD skin cell shed rate estimated in §2c.

### Foot and mouth disease virus stability in detached skin and whole-animal aerosols

While there are no studies examining the stability of FMDV in skin aerosols, there are a few studies that have examined FMDV stability in skin separated from live animals (i.e., skin not subject to in vivo antibody clearance). The available data suggest that the FMDV lifetime in detached skin is long—from days to months. Sellers et al. [6] demonstrated that FMDV concentrations in swine foot lesions did not decrease over a 24 h period. Gailiunas & Cottral [57] demonstrated that FMDV in clinically normal bovine hides consistently remained infectious (and virulent) for weeks to months in storage. These samples were either dried (20°C, 40% humidity) or salt/brine-cured (temperatures ranged from 4°C to 15°C and humidity ranged from 40 to 90%).

The two related studies that examined in situ FMDV aerosol stability of naturally generated aerosols suggest that the lifetime of naturally generated aerosols is similarly long. Sellers et al. [6] and Sellers & Herniman [58] examined the quantity of airborne FMDV in animal-holding pens (looseboxes) both prior to and after killing infected animals.
swine and cattle. Only the swine measurements are discussed in detail here as these experiments were more extensive and the FMDV signal was higher (the results for cattle also suggest a long aerosol lifetime). FMDV aerosol emissions were measured under four experimental conditions: (i) in boxes in which live swine were held, (ii) in boxes in which live swine were placed and then removed (without being killed), (iii) in boxes in which live swine were placed and then killed (bodies remained in the box), and (iv) in clean boxes in which freshly killed swine bodies were placed. Overall (non-size-resolved) airborne FMDV concentrations in swine-holding pens were observed to decrease by 10–1000-fold at 30 min and 24 h, respectively, after live animals were removed (see electronic supplementary material, table S2 for more details). Separate measurements over a 1 h time period suggest that most of the decrease in airborne infectivity was associated with large (greater than 6 \( \mu \)m) aerosols and that for small (less than 3 \( \mu \)m) aerosols infectivity decreased less than 10-fold over a 1 h time period. Gravitational settling of suspended aerosols could explain such loss rates – indicating a limited loss rate (much less than 10-fold in 1 h) of FMDV infectivity in airborne aerosols.

It is important to note that the aerosol stability estimates provided by these experiments do not provide any insight into the relative importance of the skin versus respiratory emission sources. The experiments reported by Sellers et al. [6] and Sellers & Herniman [58] were performed at high (greater than 90%) relative humidity. Laboratory experiments on synthetic aerosols generated from liquid FMDV suspensions have reported high-humidity aerosol decay rates that range from near zero to 1000-fold per hour, depending on the virus strain and the suspending fluid used [59–62].

**4. DISCUSSION**

(a) Recommendations for additional experiments

The literature summarized above provides considerable evidence for the hypothesis that animal skin cells could be a significant source of infectious FMDV aerosols. However, there are important knowledge gaps. Studies are outlined below that could significantly contribute to affirming or disproving this hypothesis.

First, the FMDV concentration in the outermost skin layer that normally exfoliates (stratum corneum) needs to be characterized. This could potentially be accomplished by analysing skin samples from the bodies of infected animals using a skin surface sampling technique such as skin scraping (with care to select only the top layer of the epidermis) or skin scrubbing [63]. Follow-on work, if warranted, could characterize (i) the infectivity and stability of FMDV in these skin cells, (ii) the degree to which infectious FMD in exfoliated skin cells is intracellular versus viral rafting on the surface, (iii) the emissions rate of airborne infectious FMD skin cells, (iv) the infectious aerosols collected during whole-animal sampling and (v) the infectivity of environmentally aged (e.g. dust mite-processed) skin aerosols.

Second, the Sellers et al. [6] and Sellers & Herniman [58] experiments should be repeated. These studies are unique (and therefore should be verified) because they are the only experiments identified that have examined (i) the FMDV aerosol emission rate from dead animals, (ii) the relative importance of respiratory versus non-respiratory emission pathways (suggested from the results of whole-animal FMDV aerosol emissions from live and dead animals) and (iii) the time series of aerosol concentrations from whole animals when animals were removed from the measurement chamber (these data were used to infer the stability of infectious FMDV in natural aerosols). Key extensions to this work include the use of domestic animals other than swine and testing in environments with lower relative humidity.

(b) Implications for foot and mouth disease control

If further testing were to support the study hypothesis, then there are a number of practical implications for FMD surveillance and control.

First, the sampling and management of settled dust could prove to be a useful tool for disease surveillance and control. Owing to (i) the potentially high stability of FMDV in skin and (ii) the high fraction of exfoliated skin fragments in settled dust, FMDV could remain detectable (and indeed potentially infectious) in dust for months or years after a primary infection. The re-aerosolization of FMDV-infected settled dust could therefore prove to be a significant concern (electronic supplementary material, Particle Suspension Mechanisms).

Second, slaughtered animals may still emit airborne FMDV via continued exfoliation of infected skin cells simply by exposure to air currents (e.g. wind) and/or external mechanical abrasion (e.g. moving animal carcasses, spraying hides with water).

Third, the current focus on swine airborne emissions (and the relative neglect of cattle and sheep emissions) may need to be revisited. It is well known that hair can trap aerosols. Of the three animals considered, pigs are known to be the highest FMD aerosol emitters and also have the lowest body hair count. Therefore, while sheep (and to a lesser extent cattle) may typically have limited ability to shed skin aerosols through their coat into the atmosphere, shearing or similar actions that disturb the coat and/or skin could theoretically release infectious FMDV aerosols well after the obvious acute clinical infection has been cleared from the animal.

(c) Implications for other diseases

If further work supports the study hypothesis with respect to FMDV, the role of skin cell aerosols in spreading other viral diseases may need to be revisited (electronic supplementary material, Other Viral Diseases). Viral disease
### Table 3. Key study findings.

<table>
<thead>
<tr>
<th>Key finding</th>
<th>Level of certainty</th>
<th>New data needed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key findings from prior studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMDV is trophic for animal skin</td>
<td>well established</td>
<td></td>
</tr>
<tr>
<td>skin is a major secondary FMD viral replication site</td>
<td>well established</td>
<td></td>
</tr>
<tr>
<td>FMDV is present both in skin lesions and in skin appearing clinically normal</td>
<td>probable</td>
<td></td>
</tr>
<tr>
<td>FMDV skin concentrations are highest in the epidermal layer</td>
<td>probable</td>
<td>FMDV concentration and infectivity of apparently normal stratum corneum samples (by species and body region)</td>
</tr>
<tr>
<td>in the normal skin growth cycle, epidermal skin cells are shed into the environment</td>
<td>well established</td>
<td></td>
</tr>
<tr>
<td>skin cells constitute a significant fraction of ambient aerosols and settled dust</td>
<td>well established</td>
<td></td>
</tr>
<tr>
<td>skin cell aerosols can deposit within the respiratory system</td>
<td>probable</td>
<td></td>
</tr>
<tr>
<td>airborne skin cells are a known vehicle for disease transmission</td>
<td>well established</td>
<td></td>
</tr>
<tr>
<td>dead animals emit infectious aerosols</td>
<td>probable</td>
<td></td>
</tr>
<tr>
<td>peak FMDV aerosol emissions are coincident with peak FMDV skin concentrations</td>
<td>well established</td>
<td></td>
</tr>
<tr>
<td>FMDV has high stability in detached (whole animal) skin</td>
<td>probable</td>
<td></td>
</tr>
<tr>
<td><strong>Key findings from this study</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>estimates of the peak FMDV-infected animal skin cell shedding rate — are comparable to measured peak whole-animal aerosol emissions</td>
<td>probable</td>
<td>skin cell shedding rates for domestic animals; updated FMDV skin concentrations</td>
</tr>
<tr>
<td>— exceed the minimum infectious dose by orders of magnitude</td>
<td>possible</td>
<td>degree to which FMDV is liberated from skin cells in the respiratory system</td>
</tr>
<tr>
<td>stability of naturally generated infectious FMDV aerosols is consistent with that expected of FMDV-infected skin aerosols</td>
<td>possible</td>
<td>confirmatory studies; conclusion based on data from a single study</td>
</tr>
<tr>
<td>the whole-animal FMDV infectious aerosol size distribution is consistent with that expected for skin cell aerosols</td>
<td>well established</td>
<td>enhanced characterization of (i) skin aerosol size distribution and (ii) infectious whole-animal FMDV aerosol size distribution</td>
</tr>
<tr>
<td><strong>Utility of study hypothesis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>may point to new methods for FMD surveillance (e.g., settled dust)</td>
<td>possible</td>
<td>stability and infectivity of FMDV in dust</td>
</tr>
<tr>
<td>potential to develop new, more effective disease control measures</td>
<td>possible</td>
<td>degree to which infectious skin cells contribute to disease transmission</td>
</tr>
<tr>
<td>may lead to new studies on the persistence of the virus in the environment</td>
<td>possible</td>
<td>analysis of settled dust and other potential environmental reservoirs</td>
</tr>
<tr>
<td>may lead to better understanding of sources and vehicles of infectious aerosols with applicability to other diseases</td>
<td>possible</td>
<td>degree to which infectious skin cells contribute to viral disease transmission</td>
</tr>
</tbody>
</table>
spread via skin cell aerosol is given minimal treatment or is entirely absent in recent literature reviews [64–66]. Given the potential for skin cells to provide protection to infectious virus against adverse environmental conditions, the management of several viral diseases may also benefit from enhanced dust surveillance and management, and skin decontamination.

5. SUMMARY AND CONCLUSIONS

There is considerable evidence in the literature to support the hypothesis that infected animal skin cells could be a significant source of infectious FMDV aerosols. Table 3 provides a summary of both key findings and suggested future research.

The author would like to express his gratitude to his wife, daughters and father for their support of this project and other individuals who graciously provided considerable advice, assistance and support: Dr Pat Hullinger at the University of California, Davis; Drs Eric Card, David Epley, Thomas Bates, Lawrence Dugan and David Rakestraw; Mr Ronald Baskett and Mrs Erica von Holtz at the Lawrence Livermore National Laboratory; Dr David Paton at the Pirbright Laboratory, Institute for Animal Health; Mr John Gloster at the UK Met Office; and the anonymous reviewers of the manuscript. The author would also like to thank the Lawrence Livermore National Laboratory librarians for their considerable assistance in obtaining the papers cited in this study.

This document was prepared as an account of work sponsored by an agency of the United States government. Neither the United States government nor Lawrence Livermore National Security, LLC, nor any of their employees, makes any warranty, expressed or implied, or assumes any legal liability or responsibility for the accuracy, completeness or usefulness of any information, apparatus, product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infringe privately owned rights. Reference herein to any product or process disclosed, or represents that its use would not infring...


