Dermal Absorption of Silver from Acticoat™ Wound Dressings

Moiemen, N.S., Shale, E., Drysdale, K.J., Smith, G., Wilson, Y.T., Rapini, R. Acticoat dressings and major burns: Systemic silver absorption. The Midlands Burn Centre, University Hospitals Birmingham Foundation Trust, United Kingdom. Epub. 2010 Oct. 18. *Burns,* **37,** 27-35 (2011). MRID 48607501.

October 20, 2011

Sequence of Presentations

- Introduction and Science Assessment

  Jessica Ryman-Rasmussen, PhD, DABT

  Health Effects Division, Office of Pesticide Programs

- Ethics Assessment

  Kelly Sherman

  Office of the Director, Office of Pesticide Programs

Introduction-1

- The Agency has pending registration applications for articles treated with nanosilver.
- The Agency is interested in conducting quantitative risk assessments for these products.
- These assessments require quantitative estimates of dermal penetration of nanosilver.

Introduction-2

- There are limited data available that quantitatively estimate dermal penetration of nanosilver. Most of these data are *in vitro* data:
  - The Agency does not consider *in vitro* dermal penetration studies as sufficiently validated for stand-alone use.
  - *In vitro* dermal penetration data are used in a weight-of-the-evidence that includes animal *in vivo* and/or human data.

Introduction-3

- A recent study by Moiemen *et al.* (2011) allows quantitative estimation of dermal penetration of silver from nanosilver in human volunteers.
- The Agency thinks that use of dermal penetration estimates for silver from nanosilver in this study would likely overestimate any dermal penetration from treated articles because:
  - Patients had severely damaged skin (major burns)
  - Calculation method for estimates assumes that all circulating serum silver results from dermal absorption of silver from the wound dressing or from silver deposited in the skin layers (and not from impaired clearance)

Use of Moiemen *et al.* Study

- The Agency is proposing to use the Moieman study, together with *in vitro* studies, in a weight-of-the-evidence to quantitatively estimate dermal penetration of silver from nanosilver applied to treated articles.
  - This is an upper-bound estimate (not a mean) and is largely based on severely damaged skin, a worst-case scenario.

Study Information

- Conducted at The Midlands Burn Centre, UK
- Study Objective:
  - Confirm the safety of Acticoat use on burns (extensive)

Test Substance

- Acticoat™ wound dressings containing SILCRYST™ silver nanoparticles
- Three layers: inner core of rayon/polyester sandwiched between two layers of silver-coated low adherent polyethylene mesh:
  - Calcium alginate-coated: 7 days antimicrobial efficacy
  - Uncoated: 3 days antimicrobial efficacy

Study Methods

- Day of/before surgery:
  - Medical history, burn details, photography, baseline serum silver, fill blood count, serum chemistry
  - General anesthesia, burn and graft donor sites infiltrated with adrenaline
    - Burns: tangentially shaved or excised
    - Grafting sites: split thickness skin (254 µm) harvested via dermatome
  - Burns and grafting sites dressed with Acticoat™
    - Surface area of wound estimated by total amount of Acticoat™ applied to wound
    - Every 7 days until "healed" (95% closure), until 42 days, or when clinician determined treatment no longer required

Endpoints

- Blood silver levels
  - Study start (baseline), every 3 days until Acticoat™ discontinued, after discontinuation of Acticoat™ (1, 3, 6, 9 months)
  - Detected by ICPMS (inductively coupled plasma mass spectroscopy)
    - Does not distinguish silver ion from silver nanoparticles
    - Detection limits in blood not given: estimated at 0.1 µg Ag^+/L based on baseline range of patients in this study and instrument detection limits described in EPA SW-846 Method 6020A
- Hematology, clinical chemistry, wound healing, clinical signs

Clinical Results-1

Table 1-Extent of burn							
Patient #	TBSA (%)	Partial thickness burn (%)	Full thickness burn (%)	Total burn (%)	Donor site[c] (%)	Graft site[c] (%)	TBSA[b] (cm^2)
1.01 25 y/o male	30	27	3	30	0	0	5971.3
1.02 43 y/o male	66	15	32	47	22	28	9099.9
1.03 56 y/o male	37	21	4	25	12	13	4887.7
1.04 22 y/o female	71	1	70	71	0[d]	26	13710.9
1.05 31 y/o male	31	22	0	22	10	11	4718.1
1.06 44 y/o male	55	18	12	30	24	16	6360.5
MEDIAN	46	20	8	31	11	14	6166

y/o = year old
TBSA = Total body surface area
[a] Percentage of TBSA affected.
[b] Estimated using patients' %TBSA, height, and weight.
[c] Percentage of total body surface area affected.
[d] The first grafting procedure for this patient used Integra™.

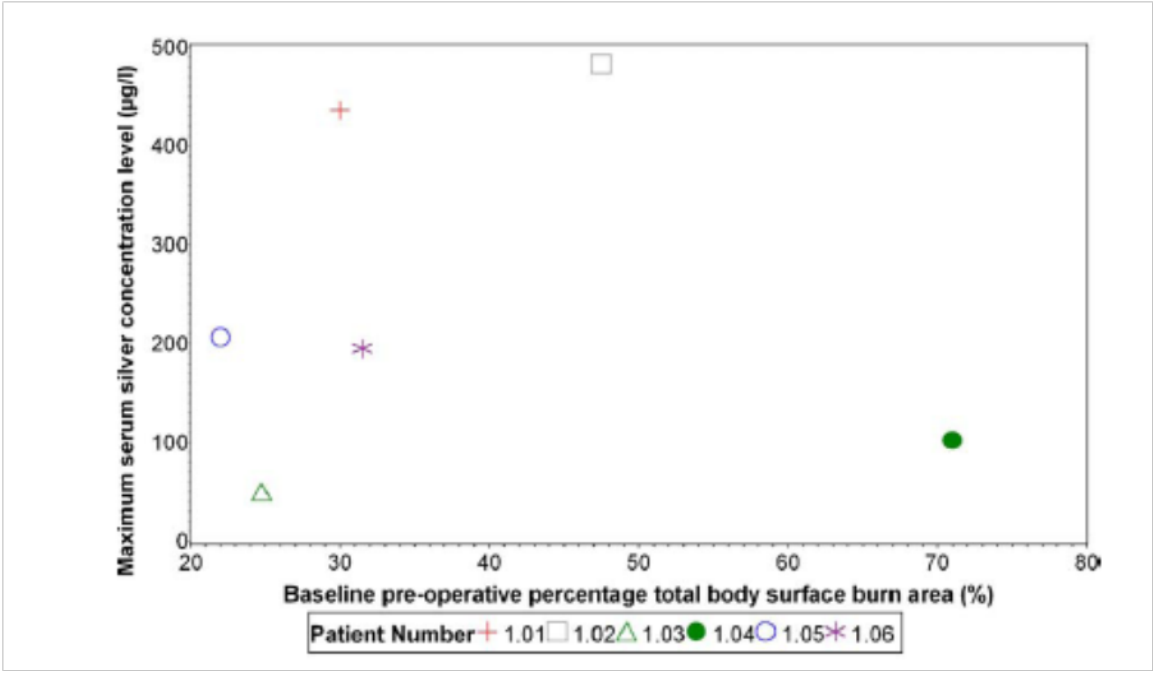
Clinical Results-2

- Hematology/clinical chemistry
  - Changes consistent with severe burns
  - Not attributed to Acticoat™
- Clinical signs
  - 32 adverse events reported, 31 unrelated
  - 1 possibly related to Acticoat™ (graft loss)
    - Not considered serious
    - Agency considers graft a restorative treatment and not a target organ of toxicity

Clinical Results-3

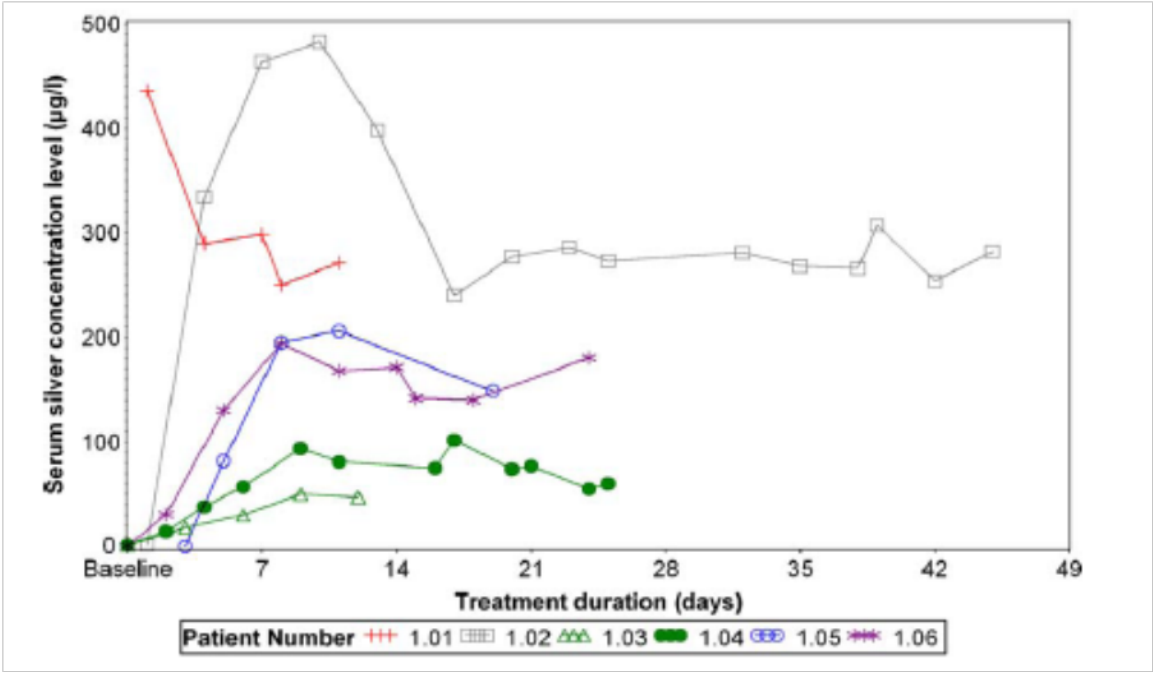
- Healing sufficient for all participants except patient 1.04
  - Patent 1.04 died: 4 serious events.
  - Withdrawn from study after grand mal seizure (fluconazole), overwhelming pseudomonas sepsis secondary to chest infection.
  - Post mortem showed brain sepsis .
- Confirmed clinican's view that Acticoat™ is safe for use on major burns

Serum Silver-During Treatment-1



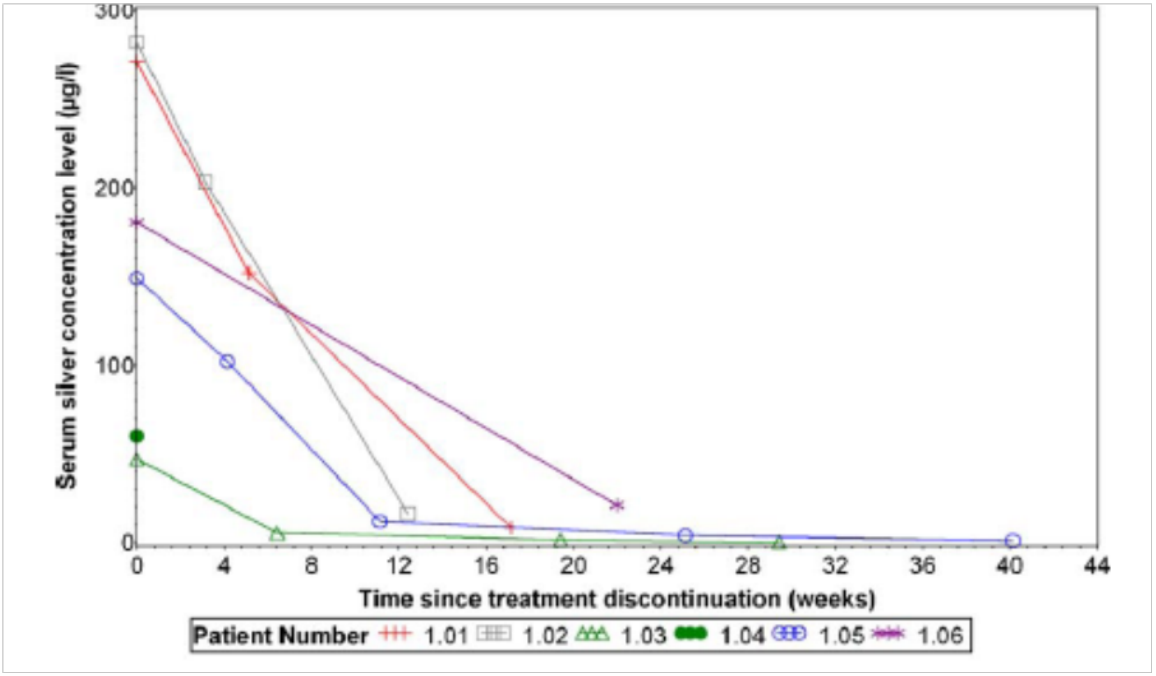
No relationship between maximum silver level and burn TBSA

Serum Silver-During Treatment-2



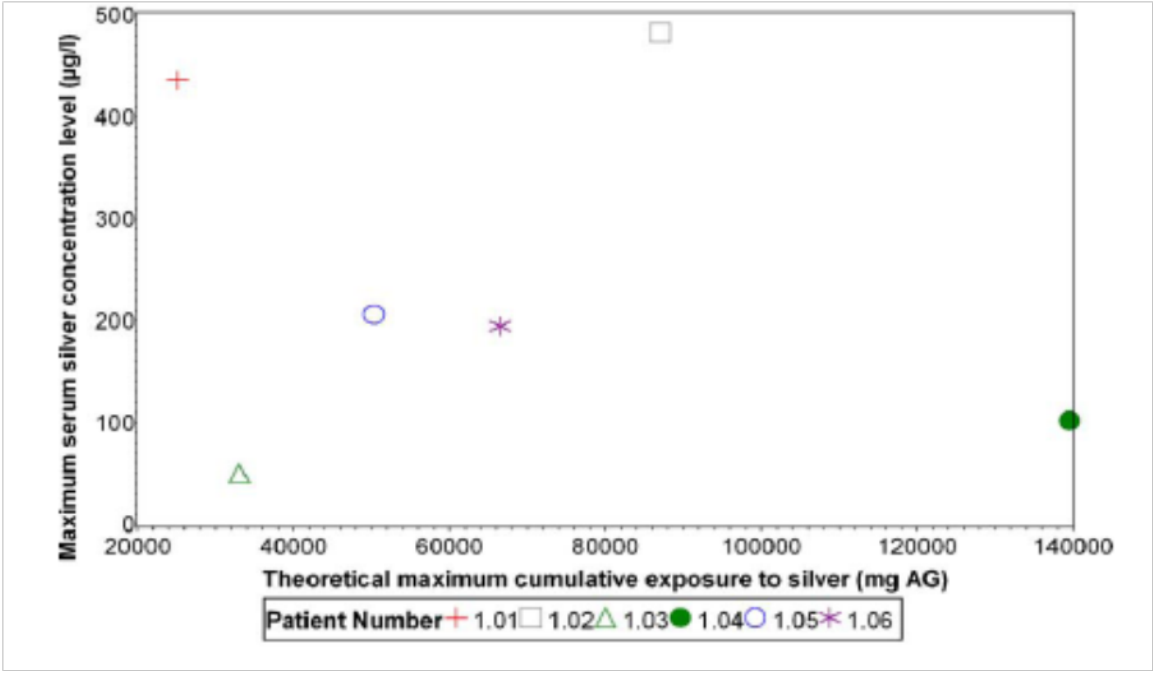
Maximum serum levels approx 9 days.
Stay at max or decay to steady-state.

Serum Silver-Discontinue Treatment



Biphasic: fast phase by 12 days.
Median half-life 46.4 days (1.5%/day).

Serum Silver-Quantify Exposure



No apparent relationship between silver exposure and maximum serum levels (could be due to burn vascularity).

Determination of Systemic Absorption of Silver from Acticoat™

- Estimated the Area Under the Curve (AUC) during treatment with wound dressing (AUC_T)
- Estimated AUC after discontinuation of wound dressing treatment (AUC_D)
- Estimated total AUC by adding AUC_T and AUC_D

Dermal Absorption Factor-1

- Divided by the total AUC by the theoretical maximum cumulative exposure to silver
- Multiplied this value by 100 to get the percentage absorbed
- Values were ≤0.1%

Dermal Absorption Factor-2

- 0.1% provides a conservative, upper-bound estimate
  - Highest value observed
  - Based on severely damaged skin
  - Calculation method assumes that all serum silver results from absorption and not from other processes (e.g. impaired clearance)
  - Orders of magnitude higher than those observed *in vitro* with intact or mildly damaged human skin

Study Limitations

- Small sample size, no statistical analysis
  - Difficult to recruit patients for this kind of study due to wound severity
- No physicochemical characterization of SILCRYST™
  - May frustrate comparison with other kinds of nanosilver because physicochemical properties not provided
- Detection limits for silver in serum for ICPMS not provided. Little detail on how ICPMS was performed.
- Calculation method for half-life of serum elimination of silver not provided.

Conclusion

Less than 0.1% penetration of silver from nanosilver is anticipated from textile products that are in direct contact with intact (healthy) skin.

Ethics Assessment of Moiemen et al. (2011)

Kelly Sherman
Office of Pesticide Programs

Introduction

- Research conducted in UK in 2006-2007, after promulgation of the 2006 Human Studies Rule
- This is considered an intentional exposure human toxicity study because it investigated the potential for adverse effects through blood biochemistry and hematology
- Study was located by EPA, not submitted to the Agency, so 40 CFR 26.1303 does not apply
  - Information for ethics review obtained from the article and information provided by the investigators

Value to Society

- This study provides data on dermal absorption of silver from nanosilver in Acticoat™ wound dressings
- EPA is currently lacking *in vivo* data on dermal absorption of silver from nanosilver
- The data could be used in EPA risk assessments for nanosilver products

Subject Selection

- Patients with burns covering greater than 20% TBSA, or their next of kin, were approached and asked about their interest in participating
- 5 men, 1 woman; aged 22-56
- Pregnancy and lactation were exclusion criteria, but pregnancy testing was not performed on the female subject
- Appropriate inclusion and exclusion criteria

Vulnerable Group

- Subjects have severe burns
- Patients with burns of this severity are extremely ill and sometimes unconscious
- Protocol provided safeguards to protect these subjects from coercion or undue influence over their decision to participate
  - 24 hours to review materials before consent solicited
  - Withdrawal permitted at any time for any reason

Risks

- No risks from use of Acticoat dressings
  - Subjects would have received the same treatment even if not enrolled in the study
- Only study-related risks were from additional blood sampling

Risk Minimization

- "Extra" blood draws were avoided where possible
  - An extra 15 mL of blood was collected when blood sampling occurred as part of normal medical treatment
- Patients likely to have sensitivity or complications were excluded. Exclusion criteria:
  - Known sensitivity to silver and other related compounds
  - Infected burns
  - Known renal, hepatic, or neurological disease
  - Known history of poor compliance with medical treatment
  - Pre-existing dementia

Benefits & Risk:Benefit Balance

- Benefits
  - No benefits to subjects
  - Societal benefit from knowledge about the safety of Acticoat when used for patients with major burns
- Risk:Benefit Balance
  - Not discussed in article
  - Risks were minimal, so the potential benefits to society outweigh the risks

Ethics Oversight

- Research was reviewed and approved by the Sandwell and West Birmingham Ethics Committee
- The committee was "fully complies" with the Standard Operative Procedures for Research Ethics Committees in the UK

Informed Consent

- Subjects (or their representatives) were provided with subject information sheet
- Provided at least 24 hours to review the information sheet
- After 24 hours, the subjects (or their representatives) were given an opportunity to discuss the study and ask questions of the investigator or research study nurse

Informed Consent—2

- 3 subjects initially signed the consent forms
- 1 subject provided verbal consent
  - Verbal consent provided in the presence of a researcher and a nurse
- 2 subjects provided consent retrospectively; their representatives initially provided consent

Respect for Subjects

- Subjects offered complete freedom to withdraw at any time for any reason
- Not paid for participation
- Subjects' privacy protected

Standards for Documentation

- The requirement at 40 CFR §26.1303 to document the ethical conduct of research submitted to EPA does not apply:
  - Study was located in the public literature, not submitted to EPA
  - EPA located the study at its own initiative

Standards of Conduct

- FIFRA §12(a)(2)(P) does not apply
  - Did not involve use of a pesticide
- 40 CFR part 26 subparts A-L do not apply
  - Neither conducted or supported by EPA
  - Not conducted with the intention to submit the results to EPA
- International Standard
  - Declaration of Helsinki (2004)

Compliance with Standards of Conduct

- Protocol states that research will be conducted in accordance with the Declaration of Helsinki
- Protocol received approval from the Sandwell and West Birmingham Local Research Ethics Committee
- Research was consensual, and was not intended to harm participants
- It appears from the published article that the conduct was consistent with the basic principles in the Declaration of Helsinki

Standards for EPA Reliance

- 40 CFR §26.1703
  - Prohibits reliance on data involving intentional exposure of pregnant or nursing women or of children
- 40 CFR §26.1705
  - Prohibits reliance on data unless EPA has adequate information to determine substantial compliance with subparts A through L for 40 CFR 26

Compliance with Standards of Acceptability

- 40 CFR §26.1703
  - All subjects were above the age of 18
  - The female subject was not pregnant or nursing
- 40 CFR §26.1705
  - EPA has adequate information to conclude that the research was conducted under procedures at least as protective as those in subparts A though L of this part

Conclusion

If it is deemed scientifically valid and relevant, there are no barriers in FIFRA or in 40 CFR §26.1703 or 26.1705 to EPA's reliance on the *Moiemen et al. (2011)* study in actions taken under FIFRA or 408 of FFDCA

Charge Questions

1. Is the Moiemen et al. (2011) study scientifically sound, providing reliable data?
2. If so, can the Moiemen et al. (2011) study be used to support the Agency's conclusion that the dermal absorption factor for silver from nanosilver on human skin is less than 0.1%?
3. Is there adequate information to support a determination that the study was conducted in substantial compliance procedures at least as protective as those at subparts A-L of 40 CFR part 26?