CHPA CONSUMER HEALTHCARE PRODUCTS ASSOCIATION
founded 1881

U.S. Food and Drug Administration
Docket No. FDA-1978-N-0018
Via electronic submission

June 27, 2019

Re: Sunscreen Drug Products for Over-the-Counter Human Use, Proposed Rule

Dear Sir or Madam,

The attached report, titled "Reports of Serious Adverse Events Associated with Spray Sunscreens in the United States Food and Drug Administration Adverse Event Reporting System Database; January 1, 2009 to December 31, 2018, was prepared by PharmaLex for CHPA". It is submitted as supporting evidence for the safety of the spray doseage form of sunscreens and is referenced in the comments filed to this docket by PCPC and CHPA.

Sincerely,

Barbara A. Kochanowski, Ph.D.
Sr. VP, Regulatory & Scientific Affairs

PHARMALEX

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Reports of Serious Adverse Events Associated with Spray Sunscreens in the United States Food and Drug Administration Adverse Event Reporting System Database
January 1, 2009 to December 31, 2018

Results Summary

For

Consumer Healthcare Products Association

Prepared by

PharmaLex US Corporation

Submitted

June 14, 2019

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Reports of Cases with Serious Adverse Events Associated with Spray Sunscreens in the United States Food and Drug Administration Adverse Event Reporting System Database January 1, 2009 to December 31, 2018: Results Summary

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I.INTRODUCTION

The United States Food and Drug Administration (FDA) has issued a proposed rule to put into effect final monograph regulations for nonprescription, over-the-counter (OTC) sunscreen drug products as required by the Sunscreen Innovation Act. The monograph will establish conditions under which FDA proposes that OTC sunscreen products are generally recognized as safe and effective (GRASE) and not misbranded. The monograph was published as part of the ongoing review of OTC drug products conducted by FDA.

To support a public comment on the proposed rule, the Consumer Healthcare Products Association (CHPA) requested PharmaLex (PLx) to conduct an analysis of the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database to establish the number of cases reporting serious adverse events ("Serious cases") related to sunscreen products, with particular interest in products that use a spray delivery mechanism (spray sunscreens).

II.OBJECTIVES

The primary objective is to determine the number of sunscreen spray product cases with serious respiratory events.

III.METHODS

FDA maintains a passive surveillance system for adverse events (AEs) associated with marketed drugs and therapeutic biological products. FAERS is the computerized database of these reports.

PLx identified a list of brand and generic sunscreen products using publicly and commercially available drug compendia, an ingredient list provided by CHPA, and other publicly available sources. The product list was used to screen FAERS for all reports for sunscreen products listed as a Primary or Secondary suspect (PS/SS) drug in reports submitted from January 1, 2009 through December 31, 2018.

The list of retrieved reports were adjudicated by a clinical pharmacist, and only those reports with confirmed sunscreen products were retained for this analysis.

The confirmed sunscreen products were further adjudicated to distinguish those using a spray delivery system. Spray products were identified by the terms "spray," "mist," "pump," or "aerosol" entered in one or more of the following FAERS fields:

- Drug name;
- Dose verbatim ;
- Dose form; or
- Dose unit.

Cases with exposures to both spray delivery and other/unknown delivery systems were excluded from the group of spray delivery products.

Selected cases were then distinguished as Serious or Non-serious. Serious cases were identified as those with a value in the FAERS Outcome field (i.e., Death, Life Threatening, Hospitalization, Disability, Congenital anomaly, Required intervention, or Other serious [important medical event]). Cases with no Outcome value were considered to be Non-serious.

Numbers of confirmed sunscreen cases stratified by seriousness (i.e., Serious, Non-serious) were separately tabulated for all reports, reports of spray delivery products only, and reports of products that do not use a spray delivery system.

For the confirmed spray delivery sunscreen cases, MedDRA version 21.1 preferred terms (PTs) included in the MedDRA System Organ Class (SOC) Respiratory, Thoracic and Mediastinal Disorders (**Appendix 1**) were reported. Of special interest was a list of pre-selected PTs associated with signs and symptoms of product inhalation: *Cough, Dyspnoea, Wheezing, Asthma, Sneezing, Choking, Choking sensation, Rhinorrhoea, Nasal congestion, Throat irritation, Obstructive airways disorder,* and *Respiratory tract irritation*. Reported PTs were also stratified by case seriousness.

IV. RESULTS

In the reporting period from January 1, 2009 through December 31, 2018, there were 28,478 FAERS reports with a confirmed sunscreen product as a PS/SS drug. Of these, 1,439 cases (5.1%) were Serious. Spray delivery products were reported in 6.2% (1,752 / 28,478) of all confirmed cases, and 145 (8.3%) of those were Serious cases (0.5% of all confirmed sunscreen cases). (**Table 1**) Note that 39 cases were exposed to sunscreen products in both spray delivery and other/unknown formulations as PS/SS drugs. Those cases were excluded from this analysis.

Table 1. Reports with Confirmed Sunscreen Products as Primary or Secondary Suspect Drugs, by Product Delivery Formulation and Seriousness: FAERS January 1, 2009-December 31, 2018

	All Forms		Spray Delivery Formulation		Other/Unknown Delivery Formulation	
Confirmed Sunscreen Cases	**N**	**%**	**N**	**%**	**N**	**%**
Cases with Sunscreen	**28,478**	***100***	**1,752**	***100***	**26,726**	***100***
Serious	1,439	*5.1*	145	*8.3*	1,294	*4.8*

	All Forms		Spray Delivery Formulation		Other/Unknown Delivery Formulation	
Confirmed Sunscreen Cases	**N**	**%**	**N**	**%**	**N**	**%**
Non-serious	27,039	*94.9*	1,607	*91.7*	25,432	*95.2*

FAERS= FDA Adverse Events Reporting System; N=Number of Cases

Sunscreen products that use a spray delivery system are of special interest because of the possibility that the active or inactive ingredients could be inhaled. **Table 2** reports all PTs within the Respiratory, thoracic and mediastinal disorders SOC that were listed in at least one of the confirmed spray delivery sunscreen product cases. As seen in the table, only 11 of the possible 534 PTs in the SOC were identified in these cases. The PTs of special interest are marked with an asterisk (*) in the table.

Of the total 1,752 cases with a confirmed spray delivery sunscreen product, 1.4% (n=25) reported one or more PTs included in the Respiratory, thoracic and mediastinal disorders SOC. These 25 cases account for 0.09% of the total 28,478 cases with any confirmed sunscreen product as a PS/SS drug. A Serious outcome was reported in 11 (44.0%) of the 25 cases.

The 11 Serious cases, reported between 2011 and 2018, comprised 6 males and 5 females. In 10/11 cases "Other" (medically important) outcome was the reason for the case being classified as Serious. One of those ten cases also reported the outcome "Life Threatening," and one case reported the outcome "Hospitalization." Likewise, in 10/11 cases the sunscreen spray product was the primary suspect drug. Data on past medical history, and the duration and treatment of the adverse event is not available in the FAERS electronic file. Specific dosage and administration data were either unavailable or insufficient to evaluate adherence to label instructions.

PTs in this SOC of interest most frequently reported among the Serious cases were *Dyspnoea* (5 cases), *Choking* (3 cases), *Cough*, *Pharyngeal oedema*, and *Asthma* (2 cases each). The list of all PTs (in any SOC) reported in confirmed spray delivery sunscreen product cases are listed by Seriousness in **Appendix 2.**

Table 2. MedDRA Preferred Terms Included in the Respiratory, Thoracic and Mediastinal Disorders SOC: FAERS January 1, 2009 - December 31, 2018

MedDRA v21.1 Preferred Terms	All Cases		Serious		Non-serious	
	N	%	N	%	N	%
Confirmed cases with spray delivery sunscreen	**1,752**		**145**		**1,607**	
Cases with PTs in Respiratory, thoracic and mediastinal disorders SOC						
Percent of all spray delivery cases†	**25**	***1.5***	**11**	***7.6***	**14**	***0.9***
Percent of cases with PTs in SOC	**25**	***100***	**11**	***100***	**14**	***100***
Dyspnoea*	7	*28.0*	5	*45.5*	2	*14.3*
Cough*	4	*16.0*	2	*18.2*	2	*14.3*
Pharyngeal Oedema	4	*16.0*	2	*18.2*	2	*14.3*
Rhinorrhoea*	4	*16.0*	.	.	4	*28.6*
Asthma*	3	*12.0*	2	*18.2*	1	*7.1*
Choking*	3	*12.0*	3	*27.3*	.	.
Throat Irritation*	3	*12.0*	1	*9.1*	2	*14.3*
Choking Sensation*	1	*4.0*	.	.	1	*7.1*
Nasal Discomfort	1	*4.0*	.	.	1	*7.1*
Pulmonary Oedema	1	*4.0*	1	*9.1*	.	.
Respiratory Tract Congestion	1	*4.0*	.	.	1	*7.1*

FAERS=FDA Adverse Events Reporting System; MedDRA=Medical Dictionary for Regulatory Activities; SOC=System Organ Class; N=Number of Cases

*Pre-selected Preferred Terms

† Denominator for percent calculations in this row are the total number of cases for the respective columns

Note: Rows are not mutually exclusive

V. DISCUSSION

Sunscreens are one of the most commonly purchased consumer skin care products. From June 2017 to June 2018, the top 10 sun protection brands totaled approximately $1.2 billion in sales and 144.7 million units sold.[1] In the 10-year period from January 1, 2009 to December 31, 2018 there were 28,478 FAERS reports associated with a confirmed sunscreen product as a Primary or Secondary suspect drug. Within the category of spray delivery products, reports totaled 1,752 over 10 years, or 6.2% of all reports associated with sunscreen products. The 145 Serious spray sunscreen cases account for only 8.3% of the 1,752 confirmed spray sunscreen reports in the 10-year period, or an average of 14.5 Serious cases annually.

A specific safety concern with spray delivery sunscreen products is the potential for harmful inhalation of active or inactive ingredients. These AEs were investigated by looking specifically at PTs from the SOC for Respiratory, thoracic and mediastinal disorders. Only 25 (1.4%) of all cases with a confirmed spray delivery sunscreen product reported one or more of these PTs during the 10-year study period, and only 11 (44.0%) of those were considered Serious cases. Those 25 cases accounted for 0.09% of the total 28,478 FAERS cases with confirmed sunscreen products of any type, and the 11 Serious cases accounted for only 0.04% of that total. Post-hoc analysis of the 11 Serious cases showed that the reported seriousness outcome was "Other" (medically important event) for 10 cases, one of those ten cases also reported a "Life-threatening" outcome, and one case reported a "Hospitalization." The FAERS electronic file did not contain enough information on dosing to determine if the products were used according to the label. Also unavailable was information on past medical history, the duration of the event, or how the event was managed. Those data might be available in the full case narratives of the MedWatch forms for these cases, which can be obtained from FDA via request through the Freedom of Information Act.

Dyspnoea was the most commonly reported of the selected PTs among the Serious cases (n=5). A total of only 11 different PTs were reported out of a possible 534 PTs included in the SOC. Thus, during the 10 years between 2009 and 2018, Serious cases of respiratory events possibly associated with the inhalation of spray sunscreens were very rarely reported (about 1 case per year). The annual number of units sold for spray sunscreens is unknown, but sales data indicate that potential users could number in the high tens of millions annually. Considering that the single brand "Banana Boat UltraMist Sport Performance" alone accounted for 8.3 million units sold[2], if exposures based on sales of all spray sunscreen products were factored together a very low rate of associated serious respiratory events would be expected.

Limitations. FAERS provides data for post-marketing surveillance and helps identify potential safety signals associated with drug use that may warrant further investigation. This analysis in FAERS involved a dataset of 28,478 case reports with a confirmed sunscreen product listed as a primary or secondary suspect drug. This number of adverse event reports over 10 years, though not necessarily

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[1] Beauty Data Dive. Drug Store News Daily. August 26, 2018.
[2] Ibid.

representative of all AEs occurring with use of these products, can provide an initial estimate of the annual number of reports that can be expected.

One limitation to consider when interpreting findings from FAERS is that spontaneous reports are subject to several reporting biases. Those biases include the length of time a product has been on the market, reporting country, reporting environment and public awareness generated by the media, medical publications, and FDA safety alerts. For example, in 2012-2013, there were media reports and an FDA safety communication warning of potential flammable ignition of some spray sunscreens in specific situations.[3] These incidents typically stimulate an increase in awareness and safety reporting for the products overall. Common to all spontaneous reporting systems is underreporting of AEs (i.e., numerator data unknown) and lack of a defined population at risk (i.e., denominator data unknown). While spontaneous reports cannot be used to estimate the incidence of an event, they do aid in the detection of safety signals. Those are patterns of adverse events that may appear when examined along with other factors such as time, geography, drug/drug classes, or subject demographics. In this analysis of FAERS, few Serious cases in spray sunscreens were reported and no evidence of a safety signal was found.

Another common limitation of spontaneous reports is the quantity and quality of information available in each case report. These data often lack important information (such as medical history, other vital signs and symptoms, concomitant medications, etc.) that would help assess a causal relationship to the suspect drug or establish alternative etiology. In general, FAERS reports do not allow for an accurate assessment of causality, and therefore there is no presumption that a specific drug was the direct cause of a reported event.

VI. CONCLUSION

An analysis of FAERS case reports for spray sunscreens for the period of January 1, 2009 through December 31, 2018 revealed 1,752 reports overall, with only 145 cases considered Serious. Only 25 cases involved a PT related to an event within the SOC for Respiratory, thoracic and mediastinal disorders, and only 11 of these were considered Serious. Using the annual number of units sold as an estimate of the overall total consumer exposure to spray sunscreens, associated respiratory events are expected to be very rare and therefore not indicative of a safety signal.

[3] Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS) between July – September 2012. Available at: https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers/potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event-reporting-system-1. Accessed: May 21, 2019.

APPENDIX 1. Preferred Terms in the MedDRA v21.1 SOC Respiratory, Thoracic and Mediastinal Disorders

MedDRA v21.1 Preferred Terms
Acquired bronchial cyst
Acquired diaphragmatic eventration
Acquired tracheo-oesophageal fistula
Acute chest syndrome
Acute interstitial pneumonitis
Acute lung injury
Acute pulmonary oedema
Acute respiratory distress syndrome
Acute respiratory failure
Adductor vocal cord weakness
Adenoidal disorder
Adenoidal hypertrophy
Airway remodelling
Allergic bronchitis
Allergic cough
Allergic pharyngitis
Allergic respiratory disease
Allergic respiratory symptom
Allergic sinusitis
Alveolar aeration excessive
Alveolar lung disease
Alveolar proteinosis
Alveolitis
Alveolitis allergic
Alveolitis necrotising
Anaemic hypoxia
Anoxia
Apnoea
Apnoeic attack
Apparent life threatening event
Asphyxia
Aspiration
Aspirin-exacerbated respiratory disease
Asthma*
Asthma exercise induced
Asthma late onset
Asthma-chronic obstructive pulmonary disease overlap syndrome

MedDRA v21.1 Preferred Terms
Asthmatic crisis
Atelectasis
Atelectasis neonatal
Atopic cough
Atrophic pharyngitis
Autoimmune lung disease
Bendopnoea
Bradypnoea
Bronchial artery aneurysm
Bronchial disorder
Bronchial dysplasia
Bronchial fistula
Bronchial haemorrhage
Bronchial hyperreactivity
Bronchial irritation
Bronchial metaplasia
Bronchial obstruction
Bronchial oedema
Bronchial polyp
Bronchial secretion retention
Bronchial ulceration
Bronchial varices
Bronchial varices haemorrhage
Bronchial wall thickening
Bronchiectasis
Bronchitis chronic
Broncholithiasis
Bronchomalacia
Bronchoplegia
Bronchopleural fistula
Bronchopneumopathy
Bronchopulmonary disease
Bronchopulmonary dysplasia
Bronchospasm
Bronchospasm paradoxical
Bronchostenosis
Caplan's syndrome
Catarrh
Cheyne-Stokes respiration

MedDRA v21.1 Preferred Terms
Childhood asthma
Choking*
Choking sensation*
Chronic eosinophilic rhinosinusitis
Chronic hyperplastic eosinophilic sinusitis
Chronic obstructive pulmonary disease
Chronic respiratory disease
Chronic respiratory failure
Chronic rhinosinusitis with nasal polyps
Chylothorax
Combined pulmonary fibrosis and emphysema
Cough*
Cough decreased
Croup noninfectious
Cyanosis central
Cyanosis neonatal
Cystic lung disease
Decreased bronchial secretion
Dependence on respirator
Diaphragm muscle weakness
Diaphragmalgia
Diaphragmatic abnormal relaxation
Diaphragmatic disorder
Diaphragmatic paralysis
Diaphragmatic rupture
Diaphragmatic spasm
Diffuse alveolar damage
Diffuse panbronchiolitis
Dry lung syndrome
Dry throat
Dysaesthesia pharynx
Dysphonia
Dyspnoea*
Dyspnoea at rest
Dyspnoea exertional
Dyspnoea paroxysmal nocturnal
Egobronchophony
Emphysema
Eosinophilic bronchitis

MedDRA v21.1 Preferred Terms
Eosinophilic pleural effusion
Eosinophilic pneumonia
Eosinophilic pneumonia acute
Eosinophilic pneumonia chronic
Eosinophilic rhinitis
Epiglottic cyst
Epiglottic erythema
Epiglottic mass
Epiglottic oedema
Epiglottis ulcer
Epistaxis
Excessive dynamic airway collapse
Fibrinous bronchitis
Gasping syndrome
Granulomatous pneumonitis
Grunting
Haemoptysis
Haemothorax
Hepatic hydrothorax
Hepatopulmonary syndrome
Hiccups
Hydrothorax
Hyperactive pharyngeal reflex
Hypercapnia
Hyperoxia
Hyperventilation
Hypocapnia
Hypopharyngeal synechiae
Hypopnoea
Hypoventilation
Hypoventilation neonatal
Hypoxia
Hypoxia intolerance
Idiopathic interstitial pneumonia
Idiopathic pneumonia syndrome
Idiopathic pulmonary fibrosis
Immature larynx
Immature respiratory system
Increased bronchial secretion

MedDRA v21.1 Preferred Terms
Increased upper airway secretion
Increased viscosity of bronchial secretion
Increased viscosity of upper respiratory secretion
Infantile apnoea
Interstitial lung disease
Intranasal hypoaesthesia
Intranasal paraesthesia
Irregular breathing
Kussmaul respiration
Laryngeal atrophy
Laryngeal cyst
Laryngeal discomfort
Laryngeal disorder
Laryngeal dysplasia
Laryngeal dyspnoea
Laryngeal erythema
Laryngeal fistula
Laryngeal granuloma
Laryngeal haematoma
Laryngeal haemorrhage
Laryngeal hypertrophy
Laryngeal infiltration
Laryngeal inflammation
Laryngeal keratotic plaque
Laryngeal leukoplakia
Laryngeal mass
Laryngeal necrosis
Laryngeal obstruction
Laryngeal oedema
Laryngeal pachyderma
Laryngeal pain
Laryngeal polyp
Laryngeal rheumatoid arthritis
Laryngeal stenosis
Laryngeal ulceration
Laryngeal ventricle prolapse
Laryngitis allergic
Laryngospasm
Laryngotracheal oedema

MedDRA v21.1 Preferred Terms
Larynx irritation
Loeffler's syndrome
Lower respiratory tract congestion
Lower respiratory tract inflammation
Lung consolidation
Lung cyst
Lung disorder
Lung hernia
Lung hyperinflation
Lung hypoinflation
Lung induration
Lung infiltration
Lung perforation
Lupus pleurisy
Lupus pneumonitis
Lymphangioleiomyomatosis
MacLeod's syndrome
Maxillary sinus pseudocyst
Meconium aspiration syndrome
Mediastinal cyst
Mediastinal disorder
Mediastinal effusion
Mediastinal fibrosis
Mediastinal haematoma
Mediastinal haemorrhage
Mediastinal mass
Mediastinal shift
Mendelson's syndrome
Middle lobe syndrome
Mouth breathing
Multifocal micronodular pneumocyte hyperplasia
Nasal adhesions
Nasal cavity mass
Nasal cavity toxicity
Nasal congestion*
Nasal crease
Nasal crusting
Nasal cyst
Nasal discharge discolouration

MedDRA v21.1 Preferred Terms
Nasal discomfort
Nasal disorder
Nasal dryness
Nasal flaring
Nasal inflammation
Nasal mucosa atrophy
Nasal mucosal discolouration
Nasal mucosal disorder
Nasal mucosal erosion
Nasal mucosal hypertrophy
Nasal mucosal ulcer
Nasal necrosis
Nasal obstruction
Nasal odour
Nasal oedema
Nasal polyps
Nasal pruritus
Nasal septum deviation
Nasal septum disorder
Nasal septum haematoma
Nasal septum perforation
Nasal septum ulceration
Nasal turbinate abnormality
Nasal turbinate hypertrophy
Nasal ulcer
Nasal valve collapse
Nasal varices
Nasopharyngeal polyp
Nasopharyngeal reflux
Necrotising bronchiolitis
Negative pressure pulmonary oedema
Neonatal alveolar aeration excessive
Neonatal anoxia
Neonatal asphyxia
Neonatal aspiration
Neonatal hypoxia
Neonatal respiratory acidosis
Neonatal respiratory alkalosis
Neonatal respiratory arrest

MedDRA v21.1 Preferred Terms
Neonatal respiratory depression
Neonatal respiratory distress
Neonatal respiratory distress syndrome
Neonatal respiratory failure
Neonatal tachypnoea
Neuroendocrine cell hyperplasia of infancy
Nocturnal dyspnoea
Non-cardiogenic pulmonary oedema
Noninfective bronchitis
Obliterative bronchiolitis
Obstetrical pulmonary embolism
Obstructive airways disorder*
Occupational asthma
Oesophagobronchial fistula
Organic dust toxic syndrome
Organising pneumonia
Oropharyngeal blistering
Oropharyngeal cobble stone mucosa
Oropharyngeal discolouration
Oropharyngeal discomfort
Oropharyngeal dysplasia
Oropharyngeal oedema
Oropharyngeal pain
Oropharyngeal plaque
Oropharyngeal scar
Oropharyngeal spasm
Oropharyngeal swelling
Orthopnoea
Painful respiration
Paranasal cyst
Paranasal sinus discomfort
Paranasal sinus haematoma
Paranasal sinus haemorrhage
Paranasal sinus hypersecretion
Paranasal sinus hyposecretion
Paranasal sinus mucosal hypertrophy
Paranasal sinus necrosis
Paraneoplastic pleural effusion
Pharyngeal cyst

MedDRA v21.1 Preferred Terms
Pharyngeal disorder
Pharyngeal dyskinesia
Pharyngeal enanthema
Pharyngeal erosion
Pharyngeal erythema
Pharyngeal exfoliation
Pharyngeal exudate
Pharyngeal fistula
Pharyngeal haematoma
Pharyngeal haemorrhage
Pharyngeal hypertrophy
Pharyngeal hypoaesthesia
Pharyngeal inflammation
Pharyngeal lesion
Pharyngeal leukoplakia
Pharyngeal mass
Pharyngeal necrosis
Pharyngeal oedema
Pharyngeal paraesthesia
Pharyngeal polyp
Pharyngeal pouch
Pharyngeal stenosis
Pharyngeal ulceration
Phonasthenia
Pickwickian syndrome
Platypnoea
Pleural adhesion
Pleural calcification
Pleural cyst
Pleural disorder
Pleural effusion
Pleural fibrosis
Pleural fistula
Pleural rub
Pleural thickening
Pleurisy
Pleuritic pain
Pleurocutaneous fistula
Pleuroperitoneal communication

MedDRA v21.1 Preferred Terms
Pneumomediastinum
Pneumonia aspiration
Pneumonia lipoid
Pneumonitis
Pneumothorax
Pneumothorax spontaneous
Portopulmonary hypertension
Presbyphonia
Productive cough
Progressive massive fibrosis
Prolonged expiration
Pulmonary air leakage
Pulmonary alveolar haemorrhage
Pulmonary alveolar microlithiasis
Pulmonary amyloidosis
Pulmonary arterial hypertension
Pulmonary arteriopathy
Pulmonary artery aneurysm
Pulmonary artery dilatation
Pulmonary artery occlusion
Pulmonary artery stenosis
Pulmonary artery thrombosis
Pulmonary artery wall hypertrophy
Pulmonary calcification
Pulmonary capillary haemangiomatosis
Pulmonary cavitation
Pulmonary congestion
Pulmonary dysmaturity syndrome
Pulmonary embolism
Pulmonary eosinophilia
Pulmonary fibrosis
Pulmonary fistula
Pulmonary granuloma
Pulmonary haematoma
Pulmonary haemorrhage
Pulmonary haemosiderosis
Pulmonary hilar enlargement
Pulmonary hilum mass
Pulmonary hypertension

MedDRA v21.1 Preferred Terms
Pulmonary hypertensive crisis
Pulmonary hypoperfusion
Pulmonary infarction
Pulmonary interstitial emphysema syndrome
Pulmonary mass
Pulmonary microemboli
Pulmonary necrosis
Pulmonary nodular lymphoid hyperplasia
Pulmonary oedema
Pulmonary oedema neonatal
Pulmonary ossification
Pulmonary pain
Pulmonary pneumatocele
Pulmonary sarcoidosis
Pulmonary sensitisation
Pulmonary thrombosis
Pulmonary toxicity
Pulmonary vascular disorder
Pulmonary vascular resistance abnormality
Pulmonary vasculitis
Pulmonary vein occlusion
Pulmonary vein stenosis
Pulmonary veno-occlusive disease
Pulmonary venous thrombosis
Rales
Reactive airways dysfunction syndrome
Rebound nasal congestion
Reexpansion pulmonary oedema
Reflux laryngitis
Respiration abnormal
Respiratory acidosis
Respiratory alkalosis
Respiratory arrest
Respiratory depression
Respiratory depth decreased
Respiratory depth increased
Respiratory disorder
Respiratory disorder neonatal
Respiratory distress

MedDRA v21.1 Preferred Terms
Respiratory failure
Respiratory fatigue
Respiratory fremitus
Respiratory gas exchange disorder
Respiratory muscle weakness
Respiratory paralysis
Respiratory symptom
Respiratory tract congestion
Respiratory tract haemorrhage
Respiratory tract haemorrhage neonatal
Respiratory tract inflammation
Respiratory tract irritation*
Respiratory tract oedema
Respiratory tract ulceration
Restrictive pulmonary disease
Reversible airways obstruction
Rheumatoid lung
Rhinalgia
Rhinitis allergic
Rhinitis atrophic
Rhinitis hypertrophic
Rhinitis perennial
Rhinitis ulcerative
Rhinolithiasis
Rhinorrhoea*
Rhonchi
Shrinking lung syndrome
Silent sinus syndrome
Sinonasal obstruction
Sinus congestion
Sinus disorder
Sinus pain
Sinus perforation
Sinus polyp
Sinus polyp degeneration
Sinusitis noninfective
Sleep apnoea syndrome
Small airways disease
Sneezing*

MedDRA v21.1 Preferred Terms
Snoring
Sputum decreased
Sputum discoloured
Sputum increased
Sputum retention
Status asthmaticus
Stertor
Stridor
Suffocation feeling
Sulcus vocalis
Systemic sclerosis pulmonary
Tachypnoea
Thoracic haemorrhage
Throat clearing
Throat irritation*
Throat lesion
Throat tightness
Tonsillar atrophy
Tonsillar cyst
Tonsillar disorder
Tonsillar erythema
Tonsillar exudate
Tonsillar haemorrhage
Tonsillar hypertrophy
Tonsillar inflammation
Tonsillar ulcer
Tonsillolith
Tracheal calcification
Tracheal dilatation
Tracheal disorder
Tracheal diverticulum
Tracheal erythema
Tracheal fistula
Tracheal inflammation
Tracheal mass
Tracheal obstruction extrinsic
Tracheal oedema
Tracheal pain
Tracheal stenosis

MedDRA v21.1 Preferred Terms
Tracheal ulcer
Tracheobroncheopathia osteoclastica
Tracheobronchial dyskinesia
Tracheobronchomegaly
Tracheomalacia
Transient tachypnoea of the newborn
Trepopnoea
Upper airway necrosis
Upper airway obstruction
Upper airway resistance syndrome
Upper respiratory tract congestion
Upper respiratory tract inflammation
Upper respiratory tract irritation
Upper-airway cough syndrome
Use of accessory respiratory muscles
Vasomotor rhinitis
Velopharyngeal incompetence
Ventilation perfusion mismatch
Vocal cord atrophy
Vocal cord cyst
Vocal cord disorder
Vocal cord dysfunction
Vocal cord inflammation
Vocal cord leukoplakia
Vocal cord polyp
Vocal cord thickening
Wheezing*
Xyphoid retraction
Yawning

MedDRA=Medical Dictionary for Regulatory Activities; SOC=System Organ Class
*Pre-selected Preferred Terms

APPENDIX 2. Preferred Terms Associated with Spray Sunscreen Products by Seriousness, FAERS Database: January 1, 2009 - December 31, 2018

MedDRA v21.1 Preferred Terms	All Cases		Serious		Non-serious	
	N	%	N	%	N	%
Cases with Spray Sunscreen	**1,752**	***100***	**145**	***100***	**1,607**	***100***
Sunburn	635	*36.2*	39	*26.9*	596	*37.1*
Drug ineffective	152	*8.7*	12	*8.3*	140	*8.7*
Skin discolouration	152	*8.7*	4	*2.8*	148	*9.2*
Product quality issue	113	*6.4*	6	*4.1*	107	*6.7*
Rash	112	*6.4*	8	*5.5*	104	*6.5*
Expired product administered	104	*5.9*	2	*1.4*	102	*6.3*
Circumstance or information capable of leading to medication error	96	*5.5*	.	.	96	*6.0*
Blister	92	*5.3*	20	*13.8*	72	*4.5*
Eye irritation	86	*4.9*	3	*2.1*	83	*5.2*
Accidental exposure to product	85	*4.9*	8	*5.5*	77	*4.8*
Erythema	73	*4.2*	7	*4.8*	66	*4.1*
Pain	71	*4.1*	16	*11.0*	55	*3.4*
Burning sensation	56	*3.2*	7	*4.8*	49	*3.0*
Pruritus	53	*3.0*	5	*3.4*	48	*3.0*
Application site discolouration	52	*3.0*	1	*0.7*	51	*3.2*
Product expiration date issue	48	*2.7*	2	*1.4*	46	*2.9*
Hypersensitivity	46	*2.6*	21	*14.5*	25	*1.6*
Eye pain	45	*2.6*	4	*2.8*	41	*2.6*
Skin exfoliation	42	*2.4*	6	*4.1*	36	*2.2*
Burns second degree	31	*1.8*	13	*9.0*	18	*1.1*
Sticky skin	31	*1.8*	.	.	31	*1.9*
Product lot number issue	30	*1.7*	2	*1.4*	28	*1.7*
Rash erythematous	28	*1.6*	4	*2.8*	24	*1.5*
Urticaria	27	*1.5*	4	*2.8*	23	*1.4*
Hair colour changes	26	*1.5*	.	.	26	*1.6*
Ocular hyperaemia	26	*1.5*	1	*0.7*	25	*1.6*
Chemical burn	24	*1.4*	15	*10.3*	9	*0.6*
Skin burning sensation	24	*1.4*	3	*2.1*	21	*1.3*
Dry skin	23	*1.3*	4	*2.8*	19	*1.2*
Skin irritation	20	*1.1*	.	.	20	*1.2*
Application site pain	19	*1.1*	9	*6.2*	10	*0.6*
Discomfort	19	*1.1*	1	*0.7*	18	*1.1*
Product container issue	19	*1.1*	.	.	19	*1.2*
Rash macular	19	*1.1*	2	*1.4*	17	*1.1*
Skin reaction	18	*1.0*	3	*2.1*	15	*0.9*
Eye swelling	17	*1.0*	5	*3.4*	12	*0.7*
Burns third degree	16	*0.9*	12	*8.3*	4	*0.2*
Insomnia	16	*0.9*	3	*2.1*	13	*0.8*
Swelling face	16	*0.9*	7	*4.8*	9	*0.6*

MedDRA v21.1 Preferred Terms	All Cases		Serious		Non-serious	
	N	%	N	%	N	%
Therapeutic product ineffective	16	0.9	.	.	16	1.0
Unevaluable event	15	0.9	.	.	15	0.9
Application site burn	14	0.8	9	6.2	5	0.3
Pain of skin	14	0.8	4	2.8	10	0.6
Rash pruritic	14	0.8	1	0.7	13	0.8
Rash papular	12	0.7	1	0.7	11	0.7
Application site erythema	11	0.6	7	4.8	4	0.2
Crying	11	0.6	2	1.4	9	0.6
Rash generalised	11	0.6	2	1.4	9	0.6
Swelling	11	0.6	1	0.7	10	0.6
Feeling abnormal	10	0.6	.	.	10	0.6
Vomiting	10	0.6	3	2.1	7	0.4
Drug effect decreased	9	0.5	.	.	9	0.6
Hyperhidrosis	9	0.5	.	.	9	0.6
Screaming	9	0.5	.	.	9	0.6
Thermal burn	9	0.5	3	2.1	6	0.4
Application site rash	8	0.5	6	4.1	2	0.1
Application site vesicles	8	0.5	7	4.8	1	<0.05
Lacrimation increased	8	0.5	1	0.7	7	0.4
Product odour abnormal	8	0.5	.	.	8	0.5
Product residue present	8	0.5	.	.	8	0.5
Burns first degree	7	0.4	7	4.8	.	.
Dyspnoea*	7	0.4	5	3.4	2	0.1
Nail discolouration	7	0.4	.	.	7	0.4
Scar	7	0.4	6	4.1	1	<0.05
Skin cancer	7	0.4	7	4.8	.	.
Skin disorder	7	0.4	1	0.7	6	0.4
Skin warm	7	0.4	1	0.7	6	0.4
Accidental exposure to product by child	6	0.3	.	.	6	0.4
Heat stroke	6	0.3	.	.	6	0.4
Product physical consistency issue	6	0.3	1	0.7	5	0.3
Wrong technique in product usage process	6	0.3	2	1.4	4	0.2
Adverse reaction	5	0.3	.	.	5	0.3
Application site pruritus	5	0.3	2	1.4	3	0.2
Chemical burn of skin	5	0.3	4	2.8	1	<0.05
Chemical burns of eye	5	0.3	5	3.4	.	.
Dermatitis contact	5	0.3	4	2.8	1	<0.05
Exposure via direct contact	5	0.3	.	.	5	0.3
Eye burns	5	0.3	2	1.4	3	0.2
Feeling hot	5	0.3	2	1.4	3	0.2
Loss of personal independence in daily activities	5	0.3	1	0.7	4	0.2
Paraesthesia	5	0.3	2	1.4	3	0.2

MedDRA v21.1 Preferred Terms	All Cases		Serious		Non-serious	
	N	%	N	%	N	%
Peripheral swelling	5	0.3	4	2.8	1	<0.05
Photosensitivity reaction	5	0.3	2	1.4	3	0.2
Skin tightness	5	0.3	.	.	5	0.3
Abdominal discomfort	4	0.2	.	.	4	0.2
Application site reaction	4	0.2	2	1.4	2	0.1
Cough*	4	0.2	2	1.4	2	0.1
Dehydration	4	0.2	4	2.8	.	.
Headache	4	0.2	2	1.4	2	0.1
Liquid product physical issue	4	0.2	1	0.7	3	0.2
Nausea	4	0.2	1	0.7	3	0.2
Pharyngeal oedema	4	0.2	2	1.4	2	0.1
Product colour issue	4	0.2	.	.	4	0.2
Rhinorrhoea*	4	0.2	.	.	4	0.2
Seborrhoea	4	0.2	1	0.7	3	0.2
Skin fissures	4	0.2	.	.	4	0.2
Vision blurred	4	0.2	2	1.4	2	0.1
Adverse event	3	0.2	1	0.7	2	0.1
Application site dryness	3	0.2	.	.	3	0.2
Application site exfoliation	3	0.2	2	1.4	1	<0.05
Application site haemorrhage	3	0.2	3	2.1	.	.
Application site scab	3	0.2	3	2.1	.	.
Asthma*	3	0.2	2	1.4	1	<0.05
Choking*	3	0.2	3	2.1	.	.
Condition aggravated	3	0.2	1	0.7	2	0.1
Contusion	3	0.2	2	1.4	1	<0.05
Dermatitis acneiform	3	0.2	.	.	3	0.2
Dizziness	3	0.2	2	1.4	1	<0.05
Emotional distress	3	0.2	3	2.1	.	.
Facial pain	3	0.2	1	0.7	2	0.1
General symptom	3	0.2	.	.	3	0.2
Intercepted medication error	3	0.2	.	.	3	0.2
Limb discomfort	3	0.2	2	1.4	1	<0.05
Nonspecific reaction	3	0.2	1	0.7	2	0.1
Off label use	3	0.2	.	.	3	0.2
Oral discomfort	3	0.2	2	1.4	1	<0.05
Pain in extremity	3	0.2	.	.	3	0.2
Product administered at inappropriate site	3	0.2	.	.	3	0.2
Product physical issue	3	0.2	2	1.4	1	<0.05
Product use issue	3	0.2	1	0.7	2	0.1
Sensory disturbance	3	0.2	1	0.7	2	0.1
Skin discomfort	3	0.2	1	0.7	2	0.1
Stress	3	0.2	2	1.4	1	<0.05
Throat irritation*	3	0.2	1	0.7	2	0.1

MedDRA v21.1 Preferred Terms	All Cases		Serious		Non-serious	
	N	%	N	%	N	%
Visual acuity reduced	3	*0.2*	1	*0.7*	2	*0.1*
Visual impairment	3	*0.2*	1	*0.7*	2	*0.1*
Accident	2	*0.1*	2	*1.4*	.	.
Acne	2	*0.1*	.	.	2	*0.1*
Alopecia	2	*0.1*	.	.	2	*0.1*
Anaphylactic reaction	2	*0.1*	2	*1.4*	.	.
Auricular swelling	2	*0.1*	1	*0.7*	1	*<0.05*
Back pain	2	*0.1*	2	*1.4*	.	.
Blindness	2	*0.1*	2	*1.4*	.	.
Blister rupture	2	*0.1*	2	*1.4*	.	.
Cellulitis	2	*0.1*	2	*1.4*	.	.
Dermatitis allergic	2	*0.1*	.	.	2	*0.1*
Exposure via eye contact	2	*0.1*	2	*1.4*	.	.
Exposure via inhalation	2	*0.1*	2	*1.4*	.	.
Eyelid oedema	2	*0.1*	1	*0.7*	1	*<0.05*
Fatigue	2	*0.1*	2	*1.4*	.	.
Generalised erythema	2	*0.1*	1	*0.7*	1	*<0.05*
Hypoaesthesia	2	*0.1*	2	*1.4*	.	.
Injury	2	*0.1*	2	*1.4*	.	.
Irritability	2	*0.1*	.	.	2	*0.1*
Limb injury	2	*0.1*	2	*1.4*	.	.
Lip swelling	2	*0.1*	2	*1.4*	.	.
Malaise	2	*0.1*	2	*1.4*	.	.
Maternal exposure during pregnancy	2	*0.1*	2	*1.4*	.	.
Miliaria	2	*0.1*	.	.	2	*0.1*
Mobility decreased	2	*0.1*	2	*1.4*	.	.
Musculoskeletal pain	2	*0.1*	2	*1.4*	.	.
Neoplasm malignant	2	*0.1*	2	*1.4*	.	.
Ocular discomfort	2	*0.1*	1	*0.7*	1	*<0.05*
Papule	2	*0.1*	.	.	2	*0.1*
Pigmentation disorder	2	*0.1*	1	*0.7*	1	*<0.05*
Product administered to patient of inappropriate age	2	*0.1*	.	.	2	*0.1*
Product caught fire	2	*0.1*	2	*1.4*	.	.
Product label issue	2	*0.1*	1	*0.7*	1	*<0.05*
Product use complaint	2	*0.1*	2	*1.4*	.	.
Skin injury	2	*0.1*	.	.	2	*0.1*
Skin swelling	2	*0.1*	2	*1.4*	.	.
Somnolence	2	*0.1*	.	.	2	*0.1*
Abdominal pain	1	*<0.05*	.	.	1	*<0.05*
Adverse drug reaction	1	*<0.05*	.	.	1	*<0.05*
Agitation	1	*<0.05*	1	*0.7*	.	.
Anxiety	1	*<0.05*	1	*0.7*	.	.
Application site discomfort	1	*<0.05*	.	.	1	*<0.05*

MedDRA v21.1 Preferred Terms	All Cases		Serious		Non-serious	
	N	%	N	%	N	%
Application site injury	1	<0.05	1	0.7	.	.
Application site papules	1	<0.05	.	.	1	<0.05
Application site swelling	1	<0.05	1	0.7	.	.
Bipolar disorder	1	<0.05	1	0.7	.	.
Blood blister	1	<0.05	1	0.7	.	.
Body temperature increased	1	<0.05	.	.	1	<0.05
Burn infection	1	<0.05	1	0.7	.	.
Capillary disorder	1	<0.05	.	.	1	<0.05
Cardiovascular disorder	1	<0.05	1	0.7	.	.
Chapped lips	1	<0.05	.	.	1	<0.05
Choking sensation*	1	<0.05	.	.	1	<0.05
Conjunctival hyperaemia	1	<0.05	.	.	1	<0.05
Dermatitis	1	<0.05	1	0.7	.	.
Diplopia	1	<0.05	.	.	1	<0.05
Drug ineffective for unapproved indication	1	<0.05	.	.	1	<0.05
Dysgeusia	1	<0.05	.	.	1	<0.05
Eczema	1	<0.05	.	.	1	<0.05
Educational problem	1	<0.05	1	0.7	.	.
Ephelides	1	<0.05	.	.	1	<0.05
Erythema infectiosum	1	<0.05	.	.	1	<0.05
Exfoliative rash	1	<0.05	1	0.7	.	.
Exposure during pregnancy	1	<0.05	1	0.7	.	.
Exposure via ingestion	1	<0.05	.	.	1	<0.05
Eye colour change	1	<0.05	1	0.7	.	.
Eye disorder	1	<0.05	1	0.7	.	.
Eye haemorrhage	1	<0.05	.	.	1	<0.05
Eye injury	1	<0.05	.	.	1	<0.05
Eye pruritus	1	<0.05	.	.	1	<0.05
Eyelid disorder	1	<0.05	.	.	1	<0.05
Eyelid irritation	1	<0.05	1	0.7	.	.
Face injury	1	<0.05	1	0.7	.	.
Feeling cold	1	<0.05	.	.	1	<0.05
Folliculitis	1	<0.05	.	.	1	<0.05
Genital herpes	1	<0.05	1	0.7	.	.
Genital rash	1	<0.05	1	0.7	.	.
Head injury	1	<0.05	1	0.7	.	.
Hospitalisation	1	<0.05	.	.	1	<0.05
Hypoaesthesia oral	1	<0.05	1	0.7	.	.
Hypohidrosis	1	<0.05	.	.	1	<0.05
Immobile	1	<0.05	1	0.7	.	.
Inappropriate schedule of product administration	1	<0.05	.	.	1	<0.05

MedDRA v21.1 Preferred Terms	All Cases		Serious		Non-serious	
	N	%	N	%	N	%
Incorrect product administration duration	1	<0.05	.	.	1	<0.05
Incorrect route of product administration	1	<0.05	1	0.7	.	.
Infection susceptibility increased	1	<0.05	1	0.7	.	.
Joint range of motion decreased	1	<0.05	1	0.7	.	.
Joint swelling	1	<0.05	1	0.7	.	.
Lip blister	1	<0.05	.	.	1	<0.05
Lip dry	1	<0.05	1	0.7	.	.
Lip haemorrhage	1	<0.05	.	.	1	<0.05
Loss of consciousness	1	<0.05	1	0.7	.	.
Malignant melanoma	1	<0.05	1	0.7	.	.
Melanocytic naevus	1	<0.05	1	0.7	.	.
Metastases to bone	1	<0.05	1	0.7	.	.
Muscle spasms	1	<0.05	1	0.7	.	.
Nasal discomfort	1	<0.05	.	.	1	<0.05
Neck injury	1	<0.05	1	0.7	.	.
Neck pain	1	<0.05	1	0.7	.	.
Neuralgia	1	<0.05	1	0.7	.	.
Oedema	1	<0.05	.	.	1	<0.05
Oedema mouth	1	<0.05	1	0.7	.	.
Paradoxical drug reaction	1	<0.05	1	0.7	.	.
Paraesthesia oral	1	<0.05	1	0.7	.	.
Perfume sensitivity	1	<0.05	.	.	1	<0.05
Photophobia	1	<0.05	.	.	1	<0.05
Pneumonitis chemical	1	<0.05	1	0.7	.	.
Poisoning	1	<0.05	1	0.7	.	.
Precancerous cells present	1	<0.05	.	.	1	<0.05
Product closure issue	1	<0.05	.	.	1	<0.05
Product deposit	1	<0.05	.	.	1	<0.05
Pruritus generalised	1	<0.05	.	.	1	<0.05
Pulmonary oedema	1	<0.05	1	0.7	.	.
Pyrexia	1	<0.05	1	0.7	.	.
Rash maculo-papular	1	<0.05	.	.	1	<0.05
Rash morbilliform	1	<0.05	.	.	1	<0.05
Rash vesicular	1	<0.05	1	0.7	.	.
Respiratory tract congestion	1	<0.05	.	.	1	<0.05
Resuscitation	1	<0.05	1	0.7	.	.
Retching	1	<0.05	1	0.7	.	.
Rotator cuff syndrome	1	<0.05	1	0.7	.	.
Scab	1	<0.05	1	0.7	.	.
Seizure	1	<0.05	1	0.7	.	.
Skin atrophy	1	<0.05	.	.	1	<0.05
Skin lesion	1	<0.05	1	0.7	.	.

MedDRA v21.1 Preferred Terms	All Cases		Serious		Non-serious	
	N	%	N	%	N	%
Skin mass	1	<0.05	.	.	1	<0.05
Skin wound	1	<0.05	1	0.7	.	.
Sleep disorder due to general medical condition, insomnia type	1	<0.05	1	0.7	.	.
Solar dermatitis	1	<0.05	.	.	1	<0.05
Sweat gland disorder	1	<0.05	.	.	1	<0.05
Swollen tongue	1	<0.05	.	.	1	<0.05
Syncope	1	<0.05	1	0.7	.	.
Systemic lupus erythematosus	1	<0.05	1	0.7	.	.
Temperature intolerance	1	<0.05	1	0.7	.	.
Therapeutic response decreased	1	<0.05	.	.	1	<0.05
Therapy non-responder	1	<0.05	.	.	1	<0.05
Third degree chemical burn of skin	1	<0.05	1	0.7	.	.
Thrombosis	1	<0.05	.	.	1	<0.05
Traumatic intracranial haemorrhage	1	<0.05	1	0.7	.	.
Traumatic shock	1	<0.05	1	0.7	.	.
Tremor	1	<0.05	1	0.7	.	.
Vasculitis	1	<0.05	1	0.7	.	.
Wound secretion	1	<0.05	.	.	1	<0.05

FAERS=FDA Adverse Events Reporting System; MedDRA=Medical Dictionary for Regulatory Activities; SOC=System Organ Class; N=Number of Cases

*Pre-selected Preferred Terms

Note: Rows are not mutually exclusive.