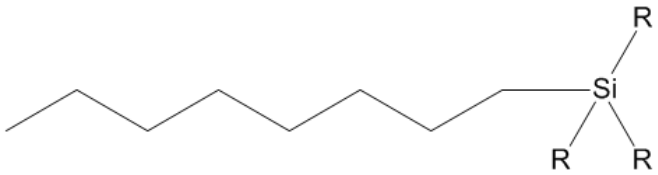
**Category:** **Waterproofing Agents** Human Health

**Definition.** Any compound that is applied to a solid surface (*e.g.*, carpets, clothing, fabrics, leather, wood, paper packaging, ceramic tiles, concrete, masonry, flooring, glass) to confer or enhance repellency or resistance to water, grease or stains is considered to be a member of this category. Of particular focus are chemicals used in consumer spray products, which may be applied without the presence of personal protective equipment.

The category includes a number of diverse sub-categories, both chemically reactive and nonreactive, given the varied structure of the active ingredients that are used in the many applications listed above. The category comprises the following sub-categories:

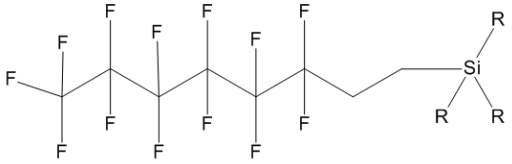
***Silanes Sub-category***

Any new chemical whose structure contains a carbon-silicon bond, and at least one other non-carbon bond to silicon, is considered to be a member of the category. The examples below provide an indication of the compounds that are included. The R-group can be an alkoxy, dimethyl (or dialkyl) amino, or halogen substituent. All three R groups are typically identical on any given member. The R' group, if present, is expected to be limited to small alkyl chains such as methyl, ethyl, or propyl. There are no restrictions on the length of the alkyl chain or its degree of branching; an example using a C8 straight chain is shown. There can be up to three of these alkyl chain attached to silicon.



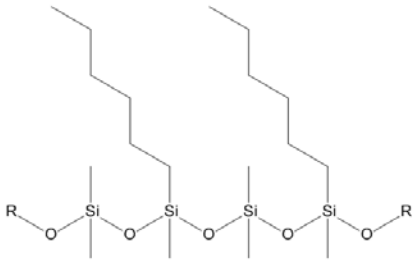

R = OR', Cl, $N(CH_3)_2$, or alkyl chain (as above) ; R' = alkyl

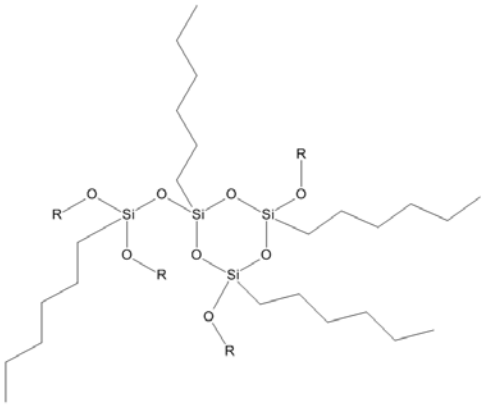
Members of this subcategory may also contain fluorinated alkyl groups. There is no restriction on the number of fluorines, which may range from one to the number required for the alkyl chain to be fully fluorinated.




***Alkoxy Silane Resins Subcategory***

Members of this category are polymeric with a variable number of repeating units containing the Si-O bond. They may be linear or cyclic; examples appear below.

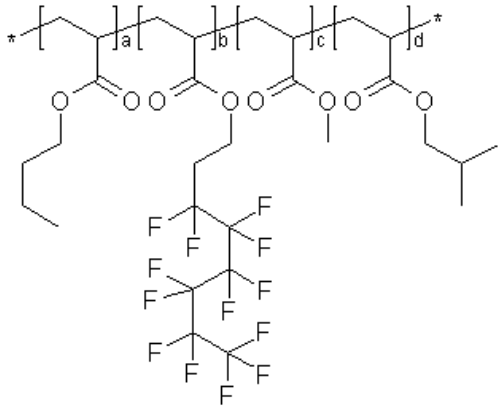




There are no limits on the size or branching of the alkyl chains. The alkyl chains may also be fluorinated or otherwise substituted. R may equal H or small alkyl groups, such as methyl, ethyl, or propyl and may be reactive.

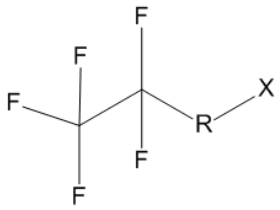
***Fluoro Acrylate Resins Sub-category***

This sub-category is comprised of polymers of acrylate (and/or methacrylate) and their corresponding fluoroalkyl ester monomers repeat units. There are no limits on the length or branching of the alkyl ester chains for the acrylate/methacrylate monomers, nor is there a limit on the length, position, or number of fluorines on the substituted monomers. There may also be more than one fluorinated monomer. The polymers are generally non-reactive, and do not have molecular weight cutoffs at either the high or low end.



***Fluorinated Surface Active Agents Sub-category***

This subcategory consists of monomeric surfactants and other surface active agents that possess a fluorinated tail and a polar head.




Where:

R = any alkyl or substituted alkyl chain, including but not limited to -$(CH_2)_n$- , -$(CF_2)_n$-, -$(CH_2CF_2)_n$-, -$(CH_2CHF)_n$-, -$O(CH_2CH_2O)_n$-, -$O(CF_2CF_2CF_2O)_n$- and so on, linear or branched.

X = any polar substituent, including –OH, -S(=O)(=O)OH, -P(=O)(OH)(OH), -C(=O)OH, -C(=O)OM (m = metal salt), -NR'R' (R' = H, or short alkyl chain, including quaternary ammonium salts).

Compounds such as $CHF_2CF_2$-R-X, $CF_3CH_2$-R-X, or $CHF_2CHF$-R-X are also members of this category.

There are no restrictions on the size of n or on the number or type of substituents present. The compounds PFOS and PFOA would be considered members of this subcategory.

**Hazard Concerns.** There is concern for acute pulmonary effects from inhalation of waterproofing chemicals. In persons exposed while using these products, respiratory symptoms, such as cough, shortness of breath and chest pain, may occur within minutes of exposure and may progress in severe cases to pulmonary edema and hemorrhage, diffuse pulmonary collapse, respiratory failure, and death. The mode of action appears to involve interference in the function of natural surfactant in the lung. Exposure levels at which effects occur vary with the specific waterproofing agent and appear to be influenced as well by other factors, such as aerosol droplet size and type of solvent present, so that no general conclusions can be drawn about effective levels in waterproofing chemicals as a class.

***Supporting Data.*** Numerous cases of acute respiratory illness have been attributed to inhalation of waterproofing materials by persons exposed during use of these products. Large outbreaks of such cases have occurred periodically, typically associated with a change in formulation of the product (*e.g.*, Hubbs et al., 1997; Vernez et al., 2006; Pauluhn et al., 2008). Respiratory symptoms, such as cough, shortness of breath, and chest pain are seen within minutes of exposure. In some cases, systemic signs, such as fever and malaise, are also reported. Frequently, affected persons have sought medical care. Chest radiographs of patients may show pulmonary infiltrates (spots resulting from fluid in the alveoli or the interstitium). Although many cases resolve spontaneously within 48 hours, supportive treatment with oxygen, bronchodilators or corticosteroids is sometimes needed. Severe cases are rare, but may include lung inflammation, pneumonia, pulmonary edema and hemorrhage, diffuse pulmonary collapse, and respiratory failure. Lethal cases have been reported in the absence of adequate ventilation or protective equipment.

Studies in laboratory animals have been performed using acute aerosol exposures, frequently by protocols meant to mimic consumer usage patterns, with short bursts of spray spaced intermittently over time periods ranging up to 3 hours. Most of these studies also included post-exposure observation periods during which the animals were monitored, ranging in duration from as short as 15 minutes up to 24 hours. One study incorporated a standard acute inhalation lethality protocol [OECD Test Guideline (TG) 403] featuring a 4-hour exposure period and 2-week observation period in order to test whether such a protocol, modified to include relevant endpoints, could be effective in identifying waterproofing products that produce respiratory impairment (Pauluhn et al., 2008). Endpoints monitored in these studies generally included respiratory function (tidal volume, respiratory rate, etc.) of the living animals using body plethysmographs before, during and after exposure; collection and analysis of bronchio-alveolar lavage fluid (BALF) from recently sacrificed animals; and/or pathological examination of the lungs of deceased animals.

With regard to respiratory function, the most notable findings following exposure to water repellents were increases in breathing rate and decreases in tidal volume and expiratory flow rate (Hubbs et al., 1997; Pauluhn et al., 2008; Norgaard et al., 2010, 2014; Larsen et al., 2014; Duch et al., 2014; Sorli et al., 2015). These effects were generally concentration-related, progressed with increasing exposure time (up to 1 hour), and did not recover after exposure stopped (up to 30 min). Arterial blood gases were measured in one study in which rats were anesthetized and mechanically ventilated (Tashiro et al., 1998). In this study, exposure to a fluorinated fabric protector produced a decrease in oxygen and increase in carbon dioxide dissolved in the arterial blood, suggesting that pulmonary gas exchange had been impaired. Changes in BALF endpoints with exposure to water repellents included increases in markers of inflammation and tissue damage (lymphocytes, neutrophils, protein, lactate dehydrogenase [LDH], gamma-glutamyl transferase [GGT]) and erythrocytes (indicating pulmonary hemorrhage) (Hubbs et al., 1997; Pauluhn et al., 2008; Norgaard et al., 2010). Increased lung weights were reported in one study (Pauluhn et al., 2008). Pathological changes in exposed animals included thickening and cellular infiltration of the alveolar septum, hyperemia of the alveolar wall, alveolar hemorrhage and edema, and alveolar collapse (atelectasis), notably without alteration of the mucous membrane of the bronchus (Yamashita and Tanaka, 1995; Yamashita et al., 1997a, 1997b; Hubbs et al., 1997; Pauluhn et al., 2008; Norgaard et al., 2010). Mortalities due to exposure were observed in several of these studies (Hubbs et al., 1997; Tashiro et al., 1998; Pauluhn et al., 2008, Norgaard et al., 2010). The changes in respiratory function and pulmonary pathology observed in *in vivo* studies have also been shown to occur with exposure to waterproofing products in an isolated perfused rat lung model (Fischer et al., 2012).

Effect levels in the available studies vary widely based on the way in which exposure concentrations were determined. Some studies reported exposure concentrations based on filter samples collected during exposure (Hubbs et al., 1997; Pauluhn et al., 2008; Norgaard et al., 2010, 2014; Larsen et al., 2014; Fischer et al., 2012), while others reported nominal levels of exposure to the whole product based on weight loss of product from the container and flow of air through the inhalation chamber (Tashiro et al., 1998; Pauluhn et al., 2008; Duch et al., 2014). As a third method, Sorli et al. (2015) reported concentrations for wet weight of product calculated from filter sample results combined with measurement of the non-volatile portion of the product. The gravimetric filter sample concentrations are much lower than the corresponding nominal

concentrations. Pauluhn et al. (2008) calculated exposure concentrations in both ways and reported nominal test concentrations of 0, 2269, 3460, 8375 and 35,283 mg/m$^3$ for a particular waterproofing product, corresponding to gravimetric filter concentrations of 0, 8.9, 9.3, 33.0, and 120.4 mg/m$^3$. While the gravimetric concentrations can be used to calculate human risk, the nominal concentrations cannot be used.

Among studies that provided concentrations in terms of whole product, effect levels varied depending on experimental protocol and the material tested. Pauluhn et al. (2008) tested several levels of Magic Nano Glass & Ceramic (containing <1% silane as active ingredient), all of which produced at least one death, identifying the low concentration of 151 mg/m$^3$ (nominal concentration was 2269 mg/m$^3$) as a LOAEL for 4-hour exposure in rats, with no NOAEL identified (other effects reported, but not necessarily at all levels, included clinical signs, respiratory function impairment, inflammatory changes evident in BALF, and pulmonary inflammation, hemorrhage and edema). Duch et al. (2014) tested levels ranging from 59 to 5700 mg/m$^3$ of Stain Repellent Super (containing alkylsiloxanes as active ingredient) in a 60-minute exposure and identified a LOAEL of 76 mg/m$^3$ and NOAEL of 59 mg/m$^3$ in mice based on respiratory function measurements (nominal concentrations). Sorli et al. (2015) used the same experimental protocol as Duch et al. (2014) to test 9 different waterproofing products. Five of the products (all alkylsilan/siloxan in ethanol or perfluorosilan/siloxan in water) produced no effect at the highest concentration tested, identifying NOAELs ranging from 259 mg/m$^3$ up to 22,161 mg/m$^3$(gravimetric concentration of the total product formulation). The other 4 products did produce acute pulmonary effects, and the NOAELs for these ranged from as high as 2958 mg/m$^3$ down to as low as 6 mg/m$^3$(gravimetric concentration of the total product formulation). The NOAEL of 6 mg/m$^3$ for whole product is the lowest effect level identified among the available studies (lower effect levels in other studies were based on filter sample concentrations that correspond to much higher whole-product concentrations). The product that had the low NOAEL of 6 mg/m$^3$ is a "Footwear Protector" containing perfluoroacrylate in water and glycol ethers. The next lowest NOAEL of 33 mg/m$^3$, from the same study, was also for a product ("Wood Impregnation") containing these ingredients.

These and other studies provide only limited information on the relative potencies of individual waterproofing compounds. Comparative studies loosely suggest that waterproofing agents containing fluorine are more toxic than those that do not (*e.g.*, Yamashita and Tanaka, 1995; Norgaard et al., 2010; Sorli et al., 2015), but this has not been rigorously demonstrated and is of uncertain generality. Within the fluorocarbon group, one study found evidence that an outbreak of respiratory disease in exposed humans was associated with a formulation change that appeared to include a shift from fluoroalkanes in the old formulation to fluoroalkenes, fluorophenyl and fluoroalcohol groups in the new formulation (Hubbs et al., 1997). Another study found that toxicity of a perfluorinated alkylsilane prepared in 3 different dilutions giving different degrees of hydrolysis increased with the degree of hydrolysis, showing that the more fully hydrolyzed derivatives were more toxic to the lung than the base chemical (Norgaard et al., 2010).

In addition to the active ingredient, waterproofing products may contain one or more solvents, stabilizers, and in some cases, propellant. They are typically applied by spraying. Studies have shown that while the active fluorocarbon or silicon compound is necessary to produce respiratory

effects, other factors also play a role. For example, the solvent can markedly influence the toxicity of the product, even when it has been shown that the solvent itself is not toxic (Norgaard et al., 2014). Also, particle size of the aerosol mist has been shown to be an important determinant of respiratory effects, with higher toxicity associated with higher percentage of respirable particles (Yamashita et al., 1997a, 1997b). Particle size (*i.e.*, the percent of respirable droplets generated) is strongly influenced by application mode (*e.g.*, brush vs pump spray vs pressurized spray can). The importance of application mode was demonstrated in a human exposure event in which misuse of a commercial product (not previously associated with effects) containing non-fluorinated alkylsiloxanes in a way that generated a high concentration of small droplets (high-pressure spray gun) resulted in acute respiratory effects, some serious, in a series of exposed workers and bystanders (Duch et al., 2014). Particle size can also be affected by solvent. However, the effects of solvent are not limited to influence on particle size. Norgaard et al. (2014) demonstrated effects of solvent on respiratory toxicity of a hydrolyzed perfluorinated siloxane with no change in particle size. In this case, using alcohols as the model solvent group, the toxicity of the perfluorinated siloxane increased with increasing carbon chain length (and lipophilicity) of the alcohol. The researchers hypothesized that the solubility of perflourosilane in the lung lining fluid increases with the quantity and lipopholicity of the solvent alcohol, and thereby facilitates contact between perfluorosilane and lung surfactant components.

It has been proposed that waterproofing sprays produce their pulmonary effects by interfering with natural surfactant in the lung (*e.g.*, Yamashita and Tanaka, 1995). Support for this hypothesis comes from several sources. Tashiro et al. (1998) found that addition of porcine surfactant to mechanically ventilated rats exposed to a fabric protector containing fluororesin partially reversed the effects of the fabric protector on blood gas levels. A companion *in vitro* study performed by the same researchers using a pulsating bubble technique showed that the fabric protector aerosol markedly increased the mean minimum surface tension of porcine surfactant, corresponding to surface tension of the alveoli at the end of expiration, to levels that can cause alveolar collapse. Other *in vitro* studies using capillary surfactometer or Langmuir-Wilhelmy film balance on porcine or bovine-derived surfactant formulations similarly found that the waterproofing products (but not solvent controls) inhibited surfactant function, measured as ability to keep the glass capillary open in the surfactometer or decreased surface pressure (increased surface tension) at maximum compression in the Langmuir film (Norgaard et al., 2014; Larsen et al., 2014; Duch et al., 2014; Sorli et al., 2015). More detailed studies by Larsen et al. (2014) showed that 1) impaired surfactant function reflected a reduction in mechanical strength of the surfactant film that could be partially reversed by adding synthetic Surfactant Peptide B (SP-B) to the mixture (synthetic SP-C was also tested but had little effect on its own and no additional effect when tested in combination with SP-B), 2) SP-B in the presence of waterproofing product relocates from the water:chloroform interface (analogous in some ways to the water:air interface in the lung) into the organic phase in water-in-chloroform emulsion, 3) SP-B forms complexes with fluorosiloxane by physical adsorption (rather than covalent binding) and this only occurs at the interface between organic and aqueous phases (not in one-phase systems), and 4) SP-B measured by binding of SP-B specific antibodies was depleted (physically or chemically modified in a way to prevent binding) in the lungs of mice exposed to waterproofing product (but not solvent controls). All of this information suggests that waterproofing agents interfere with surfactant function by physically interacting with SP-B,

inactivating it by altering its structure and removing it from its site of action, thereby weakening the surfactant film.

**Boundaries.** There are no known boundaries for these subcategories. To better define their boundaries, EPA may seek testing on members of this category that focuses on the relationship between degree of fluorination, chain length, and reactivity on limiting inhalation toxicity. Thus, this category may be modified as new information becomes available to the Agency.

**General Testing Strategy**[1]

Consistent with the amended Toxic Substances Control Act (TSCA), the multi-tiered testing methods below employ new approach methodologies (NAMs) to reduce the use of vertebrate animals in chemical testing. It incorporates *in chemico* characterization of the chemical substance in Tier I (particle size distribution, surface tension measurements) and structured *in vivo* testing from acute testing, sub-acute testing and sub-chronic testing in Tier II. It is recommended that any questions on the test strategy should be directed to the Agency.

Tier I – Use physical-chemical properties to characterize lung exposure/disruption

- Particle Size Distribution or Aerosolized Droplet Size [*i.e.*, cascade impactor, laser methods; OECD TG 110, OPPTS 830.7520, OECD Guidance Document (GD) 39].

- Surface Tension Measurements (tensiometer using the ring, stirrup or plate method or the capillary surface tension method with appropriate positive controls; ASTM D1331, ASTM D7490, ASTM D3825, OECD TG 115). The test concentrations should be 0.1%, 0.5% and 1.0%. Test concentrations representative of those at the unit operation should be tested. In addition, surface tension measurements should be done for the saturated solution concentration of chemical substances with low solubility, if appropriate.

*If respirable aerosols can be generated during manufacturing, processing, or any of the uses and surface tension increases are observed, proceed to Tier II. If not, then determine if Tier II testing is needed*

Tier II- *In Vivo* Studies

- Step 1: OECD Acute TG 403 (modified)** featuring rats exposed for 4 hours and observed for 2 weeks. Proceed to step 2 if LOAEC < 2000 mg/m$^3$.

- Step 2: 5-Day inhalation study with a 14-day recovery period** to address progression of effects (use OECD TG 412, but conduct exposure duration for at least 5 days). Proceed to step 3 if study reports substantial decrease in the point of departure over time relative to the acute study or increase in lung burden is observed.

[1] Submitters may request to use comparable test guidelines other than those listed, pending EPA's review and approval.

- Step 3: OECD TG 412**: 28-day inhalation study in rats with a 14-day recovery period

** Modifications to all above studies should include pulmonary function testing, lung burden, analysis of BALF, LDH release, blood oxygen ($pO_2$)content, and satellite reversibility. OECD TG 412 and OECD GD 39 should be consulted.

The solvent can markedly influence the toxicity of the product, even when it has been shown that the solvent itself is not toxic (Norgaard et al., 2014). This category was established for testing of waterproofing chemicals for acute pulmonary effects by inhalation exposure. Some of these chemicals may also produce subtle respiratory or systemic effects with longer-term exposure to lower concentrations or via exposure by other routes, and some of them may also fall into other new chemical categories in addition to this one. Where that situation is the case (*e.g.*, alkoxysilanes), the hazard concerns and associated testing strategies for both categories are to be taken into account.

Furthermore, the following *in vitro* test methods for cytotoxicity and irritation can provide potentially useful information:

- ICCVAM Recommended Protocol for the BALB/c 3T3/A549 lung cells Neutral Red Uptake (NRU) Cytotoxicity Test - A Test for Basal Cytotoxicity (https://ntp.niehs.nih.gov/iccvam/docs/acutetox_docs/brd_tmer/at-tmer-appxc1-508.pdf)
- ICCVAM Recommended Protocol for the Normal Human Epidermal Keratinocyte (NHK) Neutral Red Uptake (NRU) Cytotoxicity Test - A Test for Basal Cytotoxicity (https://ntp.niehs.nih.gov/iccvam/docs/acutetox_docs/brd_tmer/at-tmer-appxc2-508.pdf)
- OECD *In vitro* Skin Irritation (Test 439) – reconstructed human epidermis test method (Note: Test 404 for skin irritation and corrosion is *in vivo*).

***Supporting Data.*** The available studies provide some guidance for testing of waterproofing products for acute pulmonary effects by inhalation exposure. Pauluhn et al. (2008) demonstrated that the conventional OECD TG 403 featuring rats exposed for 4 hours and observed for 2 weeks is amenable to the comparative assessment of waterproofing products with the addition of respiratory function tests (tidal volume, expiratory flow rate, breathing rate, etc.) performed in plethysmographs before, during and after exposure, collection of BALF and analysis for differential blood cell counts and markers of tissue damage (protein, LDH, GGT and others), and gross and microscopic lung pathology. Vernez et al. (2006) emphasize the need to include sensitive markers of pulmonary function and inflammation (*i.e.*, plethysmograph measurements and BALF collection and analysis) when testing these products. Although Pauluhn et al. (2008) tested multiple exposure concentrations of one of their test materials, studies incorporating these elements have frequently been done as limit tests at high single exposure levels (Fischer et al., 2012). It has been recommended that new waterproofing agents be tested in the mixture that will be marketed, and that a wide range of particle sizes be tested to account for various application methods that might be used (Vernez et al., 2006; Pauluhn et al., 2008; Sorli et al., 2015).

Studies have been performed with the goal of developing *ex vivo* or *in vitro* models in order to reduce the number of animals subjected to product testing, with varying degrees of success (Fischer et al., 2012; Sorli et al., 2015). It has been demonstrated that the mechanism for pulmonary effects by waterproofing products involves inhibition of surfactant function (see discussion above). Sorli et al. (2015) tested 9 commercially available waterproofing sprays (at multiple dilutions) for effects on function of bovine surfactant, as evaluated in a capillary surfactometer, and compared the results to *in vivo* plethysmograph findings. They found that the *in vitro* results were highly predictive of *in vivo* toxicity. All 4 materials that were found to be toxic *in vivo* also affected surfactant function *in vitro*, and at low concentrations. Among the 5 materials that were not active *in vivo*, 2 were identified as inactive *in vitro* and 2 others were active only at high concentrations not likely to be achieved in the alveoli *in vivo*. The authors offer that this study presents a proof-of-principle for using pulmonary surfactant inhibition *in vitro* as a predictor for toxicity of inhaled waterproofing products *in vivo*, while also noting limitations of the method used (*e.g.*, limitation to water-based or water-soluble products). They suggest that *in vitro* screening might be useful as a preliminary step in advance of *in vivo* screening during product formulation, with products that fail the *in vitro* screen going back for reformulation and only products that pass the *in vitro* screen going on to *in vivo* testing.

**References.**


Duch, P., et al. (2014). Pulmonary toxicity following exposure to a tile coating product containing alkylsiloxanes. A clinical and toxicological evaluation. Clinical Toxicology (Philadelphia, Pa.) 52(5): 498-505.

Fischer, M., et al. (2012). A pilot study on the refinement of acute inhalation toxicity studies: the isolated perfused rat lung as a screening tool for surface-active substances. Alternatives to Laboratory Animals: ATLA 40(4): 199-209.

Hubbs, A. F., et al. (1997). Acute lung injury induced by a commercial leather conditioner. Toxicology and Applied Pharmacology 143(1): 37-46.

Larsen, S. T., et al. (2014). Mechanism of action of lung damage caused by a nano-film spray product. Toxicological Sciences: official journal of the Society of Toxicology 140(2): 436-444.

Norgaard, A. W., et al. (2014). Pulmonary toxicity of perfluorinated silane-based nanofilm spray products: solvent dependency. Toxicological Sciences: official journal of the Society of Toxicology 137(1): 179-188.

Norgaard, A. W., et al. (2010). Lung damage in mice after inhalation of nanofilm spray products: the role of perfluorination and free hydroxyl groups. Toxicological Sciences: official journal of the Society of Toxicology 116(1): 216-224.

Pauluhn, J., et al. (2008). Assessment of early acute lung injury in rats exposed to aerosols of consumer products: attempt to disentangle the "Magic Nano" conundrum. Inhalation Toxicology 20(14): 1245-1262.

Sorli, J. B., et al. (2015). An *in vitro* method for predicting inhalation toxicity of impregnation spray products. ALTEX 32(2): 101-111.

Tashiro, K., et al. (1998). Mechanism of acute lung injury caused by inhalation of fabric protector and the effect of surfactant replacement. Intensive Care Medicine 24(1): 55-60.

Vernez, D., et al. (2006). Acute respiratory syndrome after inhalation of waterproofing sprays: a posteriori exposure-response assessment in 102 cases. Journal of Occupational and Environmental Hygiene 3(5): 250-261.

Yamashita, M. and J. Tanaka (1995). Pulmonary collapse and pneumonia due to inhalation of a waterproofing aerosol in female CD-1 mice. Journal of Toxicology. Clinical Toxicology 33(6): 631-637.

Yamashita, M., et al. (1997a). Mist particle diameters are related to the toxicity of waterproofing sprays: comparison between toxic and non-toxic products. Veterinary and Human Toxicology 39(2): 71-74.

Yamashita, M., et al. (1997b). Toxicity of waterproofing spray is influenced by the mist particle size. Veterinary and Human Toxicology 39(6): 332-334.

## APPENDIX 1: Search Strategy

Computerized literature searches were conducted in PubMed in November 2016 to obtain studies related to the pulmonary effects of waterproofing chemicals. The search query string is presented in Table 1.

**Table 1. Summary of detailed search strategies for waterproofing chemicals**

| **Database** Search Date | **Query String** |
|---|---|
| **PubMed** | |
| 11/15/2016 | ("inhalation exposure"[mh] OR aerosols[mh]) AND (aerosols[mh] OR pulmonary surfactants[mh] OR Surface-Active Agents[mh] OR polymers[mh] OR fluorocarbon[mh]) AND ((Lung[mh] OR "lung diseases"[mh] OR "Respiratory Tract Diseases"[mh:noexp] OR "inhalation exposure"[mh]) AND (to[sh] OR ae[sh])) AND (waterproof*[tw] OR impregnat*[tw] OR repellent[tw] OR coating[tw] OR non-absorb*[tw] OR "film-forming"[tw] OR protector[tw] OR conditioner[tw] OR siloxane[tw] OR spray[tw]) |

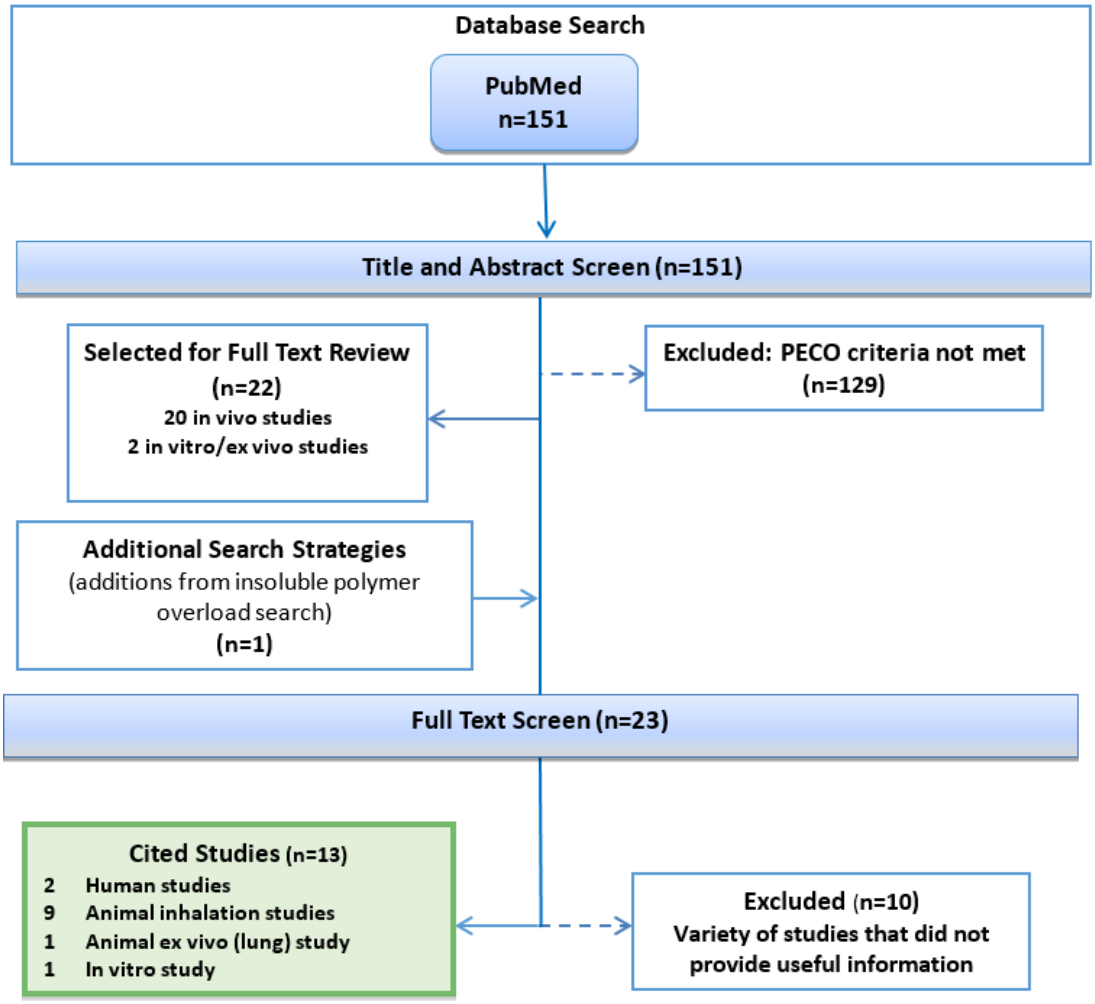
Screening methods for this search include manual screening of titles/abstracts and screening of full text articles using the eligibility criteria shown in Table 2.

**Table 2. Eligibility criteria for screening of literature search results for waterproofing chemicals**

| **PECO element** | **Evidence** |
|---|---|
| **P**opulation | Humans, laboratory animals (rats, mice, hamsters, guinea pigs, dogs, non-human primates, or other inbred mammals) and mammalian cell lines |
| **E**xposure | *In vivo* (all routes), ex vivo (isolated perfused lung) and *in vitro* |
| **C**omparison | Any comparison (across dose, duration, or route) or no comparison (*e.g.*, case reports without controls) |
| **O**utcomes | Any examination of:<br>• Pulmonary effects *in vivo* or ex vivo studies<br>• Cytotoxicity or alternative methods in *in vitro* studies |

The results of the literature screening for waterproofing chemicals are presented graphically in Figure 1. The database search results were supplemented by a review of the reference lists from relevant publications (*i.e.*, tree searching)[2] and addition of relevant studies from the literature search for polymer lung overload (1 reference). The studies that were excluded after full-text review (n=10) included a variety of studies that did not provide useful information.

**Figure 1. Literature search and screening flow diagram**




[2] This is also referred as backward reference searching.