ACUTE RESPIRATORY SYNDROME AFTER INHALATION OF WATERPROOFING SPRAYS : *A POSTERIORI* EXPOSURE-RESPONSE ASSESSMENT IN 102 CASES

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ABSTRACT

Waterproofing agents are widely used to protect leather and textiles in both domestic and occupational activities. An outbreak of acute respiratory syndrome following exposure to waterproofing sprays occurred during the winter 2002-2003 in Switzerland. About 180 cases were reported by the Swiss Toxicological Information Centre between October 2002 and March 2003, whereas less than 10 cases per year had been recorded previously. The reported cases involved 3 brands of sprays containing a common waterproofing mixture, which underwent a formulation change in the months preceding the outbreak.

A retrospective analysis was undertaken in collaboration with the Swiss Toxicological Information Centre and the Swiss Registries for Interstitial and Orphan Lung Diseases to clarify the circumstances and possible causes of the observed health effects. Individual exposure data was generated with questionnaires and experimental emission measurements. The collected data was used to conduct numeric simulation for 102 cases of exposure. A classical two-zone model was used to assess the aerosol dispersion in the near and far-field during spraying. The resulting assessed dose and exposure levels obtained were spread on large scales, of several orders of magnitude. No dose-response relationship was found between exposure indicators and health effect indicators (perceived severity and clinical indicators). Weak relationships were found between unspecific inflammatory response indicators (Leukocytes, C-reactive protein) and the maximal exposure concentration. The results obtained disclose a high inter-individual response variability, and suggest that some indirect mechanism(s) predominates in the respiratory disease occurrence. Furthermore, no threshold could be found to define a safe level of exposure. These findings suggest that the improvement of environmental exposure conditions during spraying alone does not constitute a sufficient measure to prevent future outbreaks of waterproofing spray toxicity. More efficient preventive measures are needed prior to the marketing and distribution of new waterproofing agents.

INTRODUCTION

Fluorinated polymers are widely used in a number of technologies requiring low surface energy, such as coating surface applications. The high electronegativity of fluorine strongly affects the molecules physical and chemical properties [1]. Amongst other effects, the presence of fluorine tends to reduce surface tension and enhance thermal and chemical stability. Fluoro-acrylate polymers, which exhibit a high stability and durability, are increasingly used in coating. Diluted into solvents of low polarity, the polymers may be used to coat various surfaces either in liquid or aerosol application (spraying).

There is strong evidence that inhalation of waterproofing spray can lead, in certain circumstances, to respiratory disorders. Outbreaks of respiratory failure following the use of waterproofing sprays occurred in Germany between 1979 and 1983 [2,3], and in the United States, Canada and Japan in 1992-1993 [4,5,6]. A recent case was also reported in Japan [7]. Each outbreak closely followed the marketing of a product, which underwent a formulation change of the solvent (to eliminate ozone-depleting solvents) and the fluorinated polymer (to increase solubility in the new solvent). Clinical and experimental findings of previous studies suggest that the reformulation of the products may have played a central role in pathogenesis because of the direct pulmonary toxicity of the new fluorinated resins or a possible increase in the amount of respirable fluororesin particles emitted [8,9]. Short-term management of previous outbreaks was mainly based on the removal of incriminated products from the market, but this strategy did not prevent new outbreaks to occur later with similar waterproofing agents. Instead, the periodical recurrence of toxicity outbreaks suggests that safety issues in the development of coating mixtures have so far followed a trial-and-error process, rather than a long-term anticipatory and preventive strategy.

A new outbreak of respiratory illness due to waterproofing sprays occurred recently in Switzerland [10, 11]. More than 180 cases were reported between October 2002 and March 2003, whereas 10 cases per year had been observed in the previous years. Although various commercial products were involved, they had a common waterproofing agent: a mixture of fluorinated polymer and isoparaffinic hydrocarbons, which

underwent a formulation change in both solvent and polymer shortly prior to the outbreak. Unlike the former one, the new polymer is a fluoro-acrylate polymer. The same waterproofing agent appeared to be involved in a simultaneous outbreak reported in the Netherlands [12] and in a fatal case reported from France [13]. A fatal case occurred also in the UK [14] at about the same period and under similar conditions.

Most of the incidents observed in Switzerland occurred after domestic activities, following the application of leather and textile waterproofing sprays. Three occupational cases following the use of a stain-repellent resin on stone-tiled walls and floors were also reported [15]. The exposure conditions of these three cases were investigated in a previous study [16]. Emission measurements and simulations indicated that: (1) significant aerosol and solvent concentrations may occur during waterproofing, and that (2) the amounts of solvent and particles in the workers' breathing zone were lower with the new resin formulation. This last result strongly suggests that the respiratory illness is related to the fluorinated polymer itself rather than to an increase of the exposure level to solvents and particles.

The toxic mechanism involved is unclear and several hypotheses can be suggested. On the one hand, a direct mechanism may be hypothesised. The polymer particles may exert their waterproofing effect on the alveolar surface, thereby increasing alveolar surface tension, counteracting the effect of surfactant, and leading to alveolar collapse and impairment in gas exchange as previously suggested [17]. This hypothesis is somehow supported by the polymer stability and the absence of a polymerisation reaction during the formation of the coating layer (evaporation only). On the other hand, an indirect mechanism requiring a metabolic activation with or without interaction with other factors (i.e solvents, smoking) may also take place. Previous examples of such interactions have been reported in the case of polytetrafluoroethylene (e.g. Teflon) for instance [18].

Although the commercial products involved in the Swiss outbreak have been withdrawn from the market, waterproofing agents remain widely used. Moreover, new polymers and product formulations are regularly developed and marketed. The periodical recurrence of respiratory disease observed with these products is therefore a long-term concern for both public and occupational health. Understanding the conditions under which the illness occurs is of high interest to better prevent and control future outbreaks.

The Institute of Occupational Health Sciences (IST), the Swiss Toxicological Information Centre and the Swiss Registries for Interstitial and Orphan Lung Diseases[1] undertook a joint study of the 2003 Swiss outbreak. Exposure conditions and health effects were investigated in a retrospective way through questionnaires, emission measurements and numeric simulation. The main objectives were to characterise the exposure conditions during spraying and the possible relationship between exposure and observed health effects, in order to clarify the causes of the outbreak and formulate preventive recommendations.

METHODS

Questionnaires

Following a small cluster of cases of waterproofing spray toxicity observed in one hospital, the Swiss Registries for interstitial and orphan lung diseases network (SIOLD) and the Swiss Toxicological Information Centre (STIC) were alerted and a search for other cases was initiated through national medical societies and a Swiss medical journal. The reported cases were systematically investigated through questionnaires. Each individual involved received a questionnaire covering the exposure conditions and the perceived intensity of the respiratory reaction (patient's questionnaire)[2]. The questionnaire asked for the type of waterproofing agent used (commercial name), the spraying activity (approximate spraying time, approximate amount of product used, items sprayed), the exposure environment (exposure location, room dimensions, open windows and doors, time spent in the same room after spraying) and perceived health effects (symptoms, time before occurrence, time before medical care, symptoms duration). Additional

[1] The term "orphan diseases" is used to describe >6000 disorders characterized by a very low prevalence (<1/1000 in the USA) but a severe health impairment or a threat to life. The rarity of a disorder greatly impairs all processes of disease control, such as the physician's skill to manage the disorder, scientific advances and drug availability.

[2] The questionnaire, written in French and German, is not detailed in this paper. The corresponding author may provide it upon request.

questions regarding potential contributing or confounding factors, such as smoking habits, were also included in the questionnaire.

Data on the clinical findings was collected from patients who underwent medical examination and diagnostic procedures. Patients were asked to send the medical documents in their possession (laboratory results reports, chest X-ray), and questionnaires were sent to their physicians (physician's questionnaire). Common clinical parameters were extracted from these questionnaires and documents. They included severity parameters on admission (dyspnoea levels, respiratory rate, symptoms observed, need for supplemental oxygen) as well as objective clinical parameters (C-reactive protein, white blood cells (WBC) and arterial PO_2 levels). These clinical parameters, when available, were used as severity indicators of health effects. The clinical features of the pulmonary toxicity syndrome as well as the control of the outbreak by Public Health authorities will be described in detail in forthcoming papers.

Three subjective indicators of exposure effects have been considered in this study: the delay before medical care (DELAY), the perceived symptoms (SCORE) and the dyspnoea score (DYSP). The delay before medical care depends strongly on the severity of the perceived effects from the patient's point of view. The more serious the patient believes the situation is, the more likely it is he will ask for urgent medical assistance. The symptoms reported by the patients were categorized according to the affected system: general (fever, shivers or myalgias), respiratory (cough or dyspnea), neurologic (giddiness, headache, or loss of consciousness), digestive (nausea, vomiting or abdominal pain) and Eyes/Ear-Nose-Throat (ENT) (burning eyes or throat). An arbitrary index of disease severity was used, one point was attributed to each affected system (i.e. a system for which one or more symptoms were present) and the number of systems affected was added to produce a symptom score (SCORE). Thus, a score of one indicates that symptoms were reported in only one system, while a score of five indicates that symptoms were present in all systems. The New York Heart Association dyspnoea score is a widely used medical rating of the severity of dyspnea ranging from I (shortness of breath on heavy exertion) to IV (shortness of breath at rest). The DYSP value used in this study is the dyspnoea score established during the first medical examination.

Emission rate during spraying

The amount of respirable particles emitted during spraying must be known in order to assess aerosol exposure. An estimate based on a theoretical approach is quite complex in the case of volatile aerosol emissions because key parameters, such as the diameter of droplets and their velocity, become time dependent. Moreover, the initial size distribution of the particles is strongly dependent on the physico-chemical properties of the product and the discharge conditions (pressure, nozzle size). Because of this, the use of theoretical models, such as the one proposed by Flynn[19] to predict transfer efficiency from compressed air spray guns during painting, is limited in this case. The spray cans used in our study may indeed differ significantly from air spray guns.

Figure 1 about here

An experimental approach, based on the measurement of the overspray, was therefore used. The experiment was similar to the one used to assess the transfer efficiency of the nebulizer-spray proposed by Tan and Flynn. [20]. The spraying was performed in a 7.9 m^3 experimental chamber with a constant descending laminar airflow (Figure 1). The air renewal of the experimental chamber reached a 9.7 air change per hour. During the spraying, the large particles impacted on the ground surface while the smaller particles, constituting the overspray mist, escaped through the perforated floor plate. Overspray aerosol concentrations C(t) were measured in the exhaust duct at a downstream distance of about 5 meters. It was assumed that, at this point, the volatile compounds of the particles had evaporated during the transport process [16]. Aerosol concentrations and distribution were measured with a light-scattering device: a Grimm Dust Monitor (model 1.102, Labortechnik GmbH, Ainring, Germany).

The experimental chamber was separated from the laboratory by airtight doors, and a slight depression (10 Pa) was maintained in it to avoid any leakage during the experiment. An airtight glove system allowed the experimenter to use the spray from outside. As shown in Figure 2, the spray was introduced into the chamber using repetitive short emission pulses. This “discontinuous emission” procedure was intended to avoid a significant temperature drop of the spray cans, which decreases the emission rate. It is also

considered advantageous because it lengthens the possible duration of the experiment per spray can. As shown in Figure 2, the instantaneous emission rate E_i [mg/s] may easily be deduced from the cycle time (t_1) and emission time (t_2): $E_i = \frac{t_1}{t_2} \cdot E$ (Equation 1).

Figure 2 about here

As very few of the original cans were available, preliminary experiments were therefore performed with commercial waterproofing sprays currently available on the market. These tests aimed to define the measurement protocol and set up the experimental parameters. A 5 seconds cycle time (t_1) was chosen. Each 5 seconds, a short spray pulse was emitted into the chamber. The experiment was recorded on a digital camera (DCR-TRV7E, Sony Corporation, Japan) and analysed in slow motion replay. The average pulse duration obtained (emission duration, t_2) was 0.42 seconds. By using these parameters, steady state conditions are achieved in about 10 minutes. At this point, the concentration in the exhaust duct reaches a constant value and the emission rate may be calculated by using a simple mass balance equation.

$E = C_{duct} \cdot Q_{duct}$ (Equation 2).

The preliminary experiments were also used to validate the aerosol measurement method. Results obtained from the Grimm Dust Monitor were compared with those of a Personal Data Ram (PDR, global concentration) and of an Andersen impactor (particle distribution). The average variations for fine particles (<10µm) were 12.6 % for the PDR and 8.9 % for the Andersen. These differences are not relevant in comparison with the uncertainties of other simulation parameters (such as the spraying time), which were established on the basis of patient's questionnaires. Moreover, they may easily be explained by the slight difference in the working ranges between the measuring devices.

Modelling of exposure concentrations.

As the health effects observed were essentially located at the pulmonary alveolar level [11,15], our concern regarding particulate matter was limited to respirable aerosols (<10 μm). Due to their limited mass and size, fine particles are not affected significantly by the gravitation and aerodynamic forces shortly after their emission and thus, behave in a similar way to gases with regard to their transportation and dispersion. Classical gas dispersion models can therefore be used to assess the respirable aerosol concentrations in the breathing zone at the time of exposure.

The well-known *Two-Compartment Model* (Figure 3) is used in this study [21]. The choice of this compartmental model is based on practical considerations. On the one hand, only models based on simple parameters, accessible through questionnaires or literature, can be used in such retrospective study. On the other hand, the simplest compartmental model, the *Well-Mixed Room Model*, which considers a uniform concentration through the room, may severely underestimate the exposure near the source [22]. The *Two-Compartment Model* considers two ideally mixed dispersion volumes: the near-field zone (NF), containing the emission source including the individuals' breathing zone, and the far-field zone (FF) representing the remaining part of the room. Near and far-field zones are interconnected by an inter-compartment flow (Q_e), which ensures the air and pollutant circulation inside the room. The model used considers air renewal in both near and far-field, although variations due to local geometrical effects, such as the spray orientation can not be taken into account. The evolution of the pollutant concentration into the two compartments is given in the following equations:

$$V_{NF} \cdot dC_{NF} = (E + Q_e \cdot C_{FF} - Q_e \cdot C_{NF}) \cdot dt \qquad \text{(equation 3)}$$

$$V_{FF} \cdot dC_{FF} = (Q_e \cdot C_{NF} - [Q + Q_e] \cdot C_{FF}) \cdot dt \qquad \text{(equation 4)}$$

Figure 3 about here

DATA FROM QUESTIONNAIRES

Patient's questionnaires were returned for 105 cases (return rate 52 %). 3 of them, in which mandatory data was missing or inaccurate, were discarded. The exposure conditions and/or clinical data reported in the 102 remaining cases were analysed. One could argue that some subjects may have wrongly attributed their symptoms to aerosol exposure, whereas the symptoms had in fact another origin, such as a viral infection. Although such a bias cannot be completely ruled out, we believe that the causality between aerosol exposure and symptoms appears extremely likely in most, if not all, cases, in view of the acute onset of symptoms after exposure, the clear temporal relationship between exposure and symptom occurrence, the absence of pre-existing diseases in most cases, the rapid improvement within days after the exposure, and the absence of an alternative explanation for the symptoms detected by the questionnaire. Despite the fair return rate of questionnaires, a lack of representativeness remains a possible bias. Individuals having endured only minor health effects may be less concerned and therefore less prone to fulfil the questionnaire.

Products

The products involved were mostly commercial spray cans intended for domestic or light occupational waterproofing activities. RapiAquaStop (Werner & Mertz GmbH, Mainz, Germany) was the most frequently involved spray (46% of cases). The two other sprays reported were K2R (K2R Produkte GmbH, Gottmadingen, Germany) and RapiIntemp (Werner & Mertz GmbH, Mainz, Germany) in respectively 27% and 12% of the cases. Several of these products were involved in all but three of the remaining cases. A combination of several products was used in the remaining cases. In two cases, the product name was not remembered or not known. One occupational exposure occurred with Patina-Fala (PATINA-FALA Beizmittel GmbH, Haar, Germany), a liquid stain-repellent mixture, when coated with a manual trigger spray. This specific case has already been addressed in a previous study[16]. The four identified products underwent a formulation change in both solvents and polymer prior to the incidents. A common

waterproofing agent was present in all of them: a mixture of fluorinated acrylate polymer and isoparaffinic hydrocarbons.

Exposure conditions

Surprisingly often, the exposures took place in an outdoor environment, 14 % occurred in open-air and 32 % in a partially open area such as a terrace or a balcony. Indoor environments were reported in 54 % of the cases. Ventilation (either natural or forced) was present in most of them (92%). No ventilation (no open door, no open window) was reported in only 8 % of the indoor cases.

The average volume of the rooms in which spraying took place was 49 m^3 (ranged between a minimum of 5.7 m^3 and a maximum of 250 m^3, in the case of a garage). 80% of the exposures took place in rooms of less than 75 m^3. The spraying times ranged from a few seconds to 90 minutes, while the residence time (time spent in the same room after the spraying activity) ranged from 0 to 12 hours. 80% of the exposure times were shorter than 20 minutes and 80% of the residence times were shorter than 25 minutes. The distribution of reported spraying duration and total exposure duration (spraying time + residence time) are shown in Figure 4. The exact duration is difficult to assess retrospectively and a significant uncertainty is to be expected with these two parameters. This uncertainty is however mitigated by the wide range of values reported, which fall within several orders of magnitude.

Figure 4 about here

Effects

Nearly all exposed individuals reported respiratory symptoms such as cough or dyspnoea (98 % of cases). 22% had digestive troubles, such as nausea, vomiting or abdominal pain. 37% experienced general symptoms like fever, shivers or myalgias. 40% had neurological troubles such as giddiness, headache or loss of consciousness. Eye or throat burning was reported in 20% of cases.

For 20 % of the exposed individuals, the symptoms were serious enough to require emergency hospital admission. Another 32% received ambulatory medical care, either from their regular physician or a hospital facility. The remaining 48% merely called the toxicological information centre, but they were not examined clinically.

The medical units carried out various diagnostic procedures. Three of them, which were frequently performed, were of particular interest in this study (each of them was performed in about 25-30 % of the cases). Two non-specific markers of inflammatory response were considered: the white blood cell count (WBC) and the serum C-reactive protein (CRP) concentration. The arterial partial oxygen pressure (PaO_2), reflecting pulmonary gas exchange, was also considered a marker of lung damage and impaired respiratory function. When diagnostic procedures were repeated several times for the same patient, the clinical value considered and discussed here below corresponds to the extreme observed (max for WBC and CRP, min for PaO_2). The white blood cell count (WBC) ranged between a minimum of 6.0 G/l (10^9 units per litre) and a maximum of 26.6 G/l with an average of 15.4 G/l (normal values 4-9 G/l). The CRP concentrations ranged between a minimum of 3 mg/dl and a maximum of 264 mg/dl with an average of 59 mg/dl (normal values <5 mg/dl). The PaO_2 while breathing room air ranged between 38 and 102 mmHg, with an average of 66 mmHg (normal values >80 mmHg).

47% of the involved individuals were active smokers, 25% were former smokers, and 28% had never smoked. Amongst the 64 cases in which a clinical assessment was available, 23% had a history of allergy, and 14% had a history of asthma or chronic obstructive pulmonary disease (COPD).

EXPERIMENTAL DATA

Emission rate during spraying

The average aerosol concentrations measured were 1.77 μg/m^3 for RapiAquaStop and 2.39 μg/m^3 for K2R. Considering an exhaust flow of 0.021 m^3/s (Q_{duct}), the amount of overspray emitted (E) may easily be obtained using Equation 2. An instantaneous overspray emission of 0.19 mg/s and 0.25 mg/s was

respectively found for RapiAquaStop and K2R. A gravimetric measurement (weighting of the spraying cans) indicated that the fraction of overspray in the total mass of emitted product was 0.073 % for RapiAquaStop and 0.124 % for K2R.

Typical particle size distribution for K2R and RapiAquaStop is shown in Figure 5 (distribution are is expressed here in mass fraction and not in particle count). Particle size distribution for both products is similar and little differences were found between the toxic products and the apparently non-toxic products marketed afterwards. Differences in overspray emission rates were found between toxic and non-toxic products, although they tend to diverge. The fraction of overspray in the emitted (non-toxic) product was higher for RapiAquaStop (about 0.15%) and lower for K2R (about 0.01%). No can of RapiIntemp, the third waterproofing spray, was available. As RapiIntemp and RapiAquaStop are comparable products delivered in similar cans, it was assumed that their emission characteristics were similar.

Figure 5 about here

In practice, the mean emission rate is lower than the instantaneous emission rate as the spray is not activated permanently. It was estimated that, during textile or leather waterproofing activities, the spray was activated about 50% of the time. A mean emission rate corresponding to 50% of the instantaneous emission measured was therefore considered in this study. A different ratio was used for 35% of the cases, where the reported spraying time was too high when compared to the amount of product available. When the spray had been obviously used less than 50% of time, the mean emission rate was adjusted according to a simple mass balance relationship (mean emission rate = amount of product used · percentage of overspray / reported spraying time).

MODEL IMPLEMENTATION

The dispersions were modelled through numerical simulations using Ithink (version 7.0.2, HPS High Performance Systems, Inc., Hanover, NH). The spray emission rates measured experimentally were introduced into the two-zone model. The spraying conditions described in the questionnaires were used to set the various parameters required in the two-zone model. The room volume, spraying time and residence time were depicted by quantitative parameters in the questionnaires and could therefore be used as such in the numeric simulation. Parameters related to the ventilation conditions (air renewal) and inter-compartment exchanges were assessed on the basis of qualitative information about the number of openings in the room (windows or doors) and their connected spaces (outdoor connection or connection with another room)[23]. The conditions reported were categorized in a reduced number of ventilation scenarios following the rules given in Table 1.

(Table 1 about here)

Two exposure times were considered to assess the breathed dose. The spraying time, during which the person was exposed to a near-field concentration, and the residence time, during which the exposure level was of a far-field concentration. A typical example of concentration and dose profile obtained from simulation is presented in Figure 6. In the case of outdoor exposures, the far-field volume was considered as infinite and the exposure during residence time was negligible.

Figure 6 about here

RESULTS AND DISCUSSION

Exposure assessment

An overview of the results obtained using the two-zone model are shown in Figure 7. The maximal concentrations assessed ranges from 0.003 mg/m^3 to 35.98 mg/m^3 (mean value 4.21 mg/m^3) while the estimated doses range from $0.2 \cdot 10^{-5}$ mg to 11.27 mg (mean value 0.657 mg). The two distributions are of approximately lognormal shapes. In a general sense, both assessed doses and concentrations exhibit wide ranges of values. The array of values is particularly large for the estimated dose, where seven orders of magnitude separate the upper and lower limits. This scattering mostly results from the variety of spraying and residence times reported in the questionnaires.

Figure 7 about here

Because of the trivial exposure model considered and the conservative assumptions made, only a limited confidence should be given to the absolute numbers. Still, their relative ranking is of utmost interest. The exposure levels obtained indicate that the respirable mists from the waterproofing sprays have a very low NOEL (No Observable Effect Level). Adverse effects may obviously occur even at exposure or dose levels corresponding to well ventilated spaces, or very short exposure times. Considering the products involved are widely marketed and only a small fraction of users reported troubles, these results suggest that a high response variability exists between exposed individuals.

This variability may be caused by individual factors amongst the spray users such as physiological, or metabolic differences. It should also be noted that the reported effects are presumably not of allergic nature. Another cause of variability is the presence of external factors related to exposure conditions. A typical example of this is the case of exposure to Teflon fumes [24], where the presence of the toxic product is triggered by a heat source. However, in this study, no heat source in the vicinity of the spraying activity was reported and smoking during or shortly after spraying was reported in only 10 out of the 102 cases.

Exposure vs. perceived effects

Subjective indicators of exposure effects were compared to exposure levels for possible correlations. These comparisons are summarized in Table 2. No significant relationship was found with the dose or the maximal concentration obtained during the retrospective assessment. These results suggest that factors other than exposure to overspray mist play a determining role in the occurrence of adverse health effects. The relationship between the parameters of basic exposure conditions (amount of product, spraying time) and the perceived effects are poor. A statistically significant correlation was found between the perceived symptoms (SCORE) and these parameters, although calculation of the regression coefficients (0.017 for spraying time and 0.001 for amount of product) indicated that the contribution of exposure conditions on symptoms occurrence was limited. Besides, the perceived effect indicators should be considered carefully because they rely heavily on subjective perception.

Table 2 about here

Exposure vs. objective clinical effects

The objective clinical indicators collected in the physician's questionnaires were compared to the assessed exposure indicators and exposure conditions. Clinical objective indicators are expressed as continuous variables, which can be more conveniently compared to the continuous exposure variables. The drawback is that such clinical investigations were only conducted for a fraction of cases (about one third), probably the most severe ones, which requested medical attention. A summary of the results obtained is given in Table 3a.

Table 3 about here

No significant correlation was found between any of the clinical indicators and the assessed doses, which seems to exclude any direct dose-response relationships. These results are supported by the lack of correlation between the clinical indicators and the amount of product used, which is also an indicator, albeit quite rough, of the potential dose. It is interesting to note that the values predicted through modelling (concentration, dose) are coherent with the results obtained for a basic parameter (amount of spray used) unaffected by the model simplifying hypothesis.

The relationship found for the maximal concentration and the spraying time is less obvious and must be considered in a more detailed way. Weak but significantly positive correlations were found between the non-specific inflammatory markers WBC and CRP and the maximal exposure concentrations Cmax. The detailed results are presented in table 3 and Figure 8. They show that WBC levels tended to be directly correlated with Cmax (LEU = 13.6846 + 0.2926 Cmax, R2=0.15, Pearson = 0.0533, Spearman = 0.0404), although no similar trend could be observed for the C-reactive protein levels .

Figure 8

A significant correlation was also found between the spraying time and the pulmonary gas exchange marker PaO_2 (table 3). Surprisingly, the relationship was positive, i.e. longer spraying times were correlated with higher PaO_2 (figure 9), i.e. better pulmonary gas exchange, whereas the opposite would have been expected. Since the spraying time plays a major role in exposure, this unexpected relationship further suggests that no straightforward mechanism exists between the observed health effects and the exposure levels to respirable particles. This lack of direct relationship is also apparent when considering the lack of correlation between dose vs. PaO_2 levels (table 3). The PaO_2 levels appears to be highly variable, particularly in the lowest dose range.

Figure 9 about here

Subcategories regarding smoking history, allergy and asthma or COPD were investigated, to determine whether individual susceptibility could explain the occurrence of toxicity features at very low exposure levels. No statistically significant differences were found within these subgroups concerning Cmax, Dose, and spraying time (Wilcoxon-Mann-Whitney Test) (Table 4). It must however be mentioned that the number of cases with objective clinical indicators is reduced, and it is therefore difficult to get clear evidence or to analyze subcategories in a consistent way. This is particularly true when considering subcategories related to the exposure environment, for which limitations of the two-compartment model used to assess doses and concentrations may play a significant role. Compartmental models are known to give rough estimates of real exposure conditions. When these models are used to make relative comparisons between exposures occurring in the same kind of environment, this drawback is mitigated. However, more model limitations are to be expected when comparing exposure conditions of varied nature (i.e outdoor v. indoor).

Table 4 about here

CONCLUSIONS & RECOMMENDATIONS

The acute respiratory syndrome associated with the 2002-2003 Swiss outbreak occurred in a wide array of exposure conditions, ranging from short to extensive spraying and from poorly ventilated rooms to open spaces. The resulting assessed dose and exposure levels obtained were spread on large scales of several orders of magnitude. The lack of dose-response correlation with both perceived severity and clinical indicators suggests that 1) it is not possible to define a threshold dose below which the incriminated sprays could be safely used, and 2) some indirect or complex mechanism(s) predominated in the occurrence of the respiratory disease. The occurrence of adverse effects is driven by factors other than the amount of respirable particles, such as: metabolic differences, interaction between particles and another chemical agent (e.g. residues from the solvent) or even the presence of nanoparticles. The solvent alone could be ruled out as the cause of toxicity because the particles reaching the alveoli are essentially made of non-volatile material [(16)]. It must be pointed out that no environmental factors (heat source due to smoking) were found to explain this high response variability and that no correlation was found between the subgroups exhibiting individual susceptibility factors (pre-existing lung disease, allergy or smoking) and the exposure conditions causing respiratory problems.

For these reasons and because of the vast array of spraying situations observed, it is unlikely that a simple improvement of the exposure conditions may have prevented the occurrence of the toxicity outbreak. Thus, enforcing the compliance with the basic safety measures, such as spraying in a well-ventilated space, is obviously not sufficient in this case. Besides, commercial products intended for domestic applications must be usable without respiratory protective equipment. A more efficient prevention should have taken place prior to the product marketing and distribution. It is interesting to note that the product toxicity was tested according to German standards prior to marketing. To our knowledge, the effects of 4-5 μm aerosol droplets were tested on rats at a high exposure concentration. However, tests conduced in such a narrow range may not have appropriately reflected the possible human health effects at the pulmonary alveolar level. It is well established that the morphological differences between rats and human affect both inhalation and deposition patterns. Moreover, retention and clearance patterns have also shown to be

species-dependant[25,26]. A smaller particle size (around 0.1 μm) would have been more appropriate to assess alveolar toxicity. Finally, alveolar inflammation and impairment of gas exchange could have taken place in rats having inhaled the product, but could have remained undetected if only animal survival was considered as an outcome, and if appropriate analyses of lung function and inflammation were not performed.

Additionally, the preventive strategy should take into account the full range of particle size which could be generated by various pressurization devices. Hence, the same waterproofing agent can be marketed in various mixtures and conditioning for a broad range of applications. A change in the product physico-chemical properties or in the spraying can design (especially the nebulization system) may have an important impact on the distribution of particle size.

In summary, we believe that new outbreaks of waterproofing spray toxicity may occur if a particular combination of fluororesin and triggering factors (solvents, nebulization system) appears in a marketed product. The potential toxicity of such a product is likely to remain undetected in the pre-marketing phase if new preventive strategies are not applied. Although they may reduce the inhaled dose, written warnings on product packages are probably insufficient to prevent the toxicity because of the apparent lack of a safe threshold dose. We therefore suggest that: 1) new waterproofing agents should be bench-tested in the final mixture in which they are intended to be marketed, 2) a wide range of distribution of particle size should be considered for testing in order to encompass interspecies differences as well as the various conditioning in which the product is intended to be marketed, and 3) animal toxicity experiments should assess sensitive markers of pulmonary function and inflammation.

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LIST OF SYMBOLS

C	Mass concentration [g/m3] [mg/m3] or [µg/m3]
	C0 incoming conc., CFF far-field conc., CNF near-field conc.
E	Emission rate [g/s] [mg/s] or [µg/s]
Q	Volumic flow [m3/s]
	Qe inter-compartment flow
t	time [s]
V	Volume [m3]

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TABLES AND FIGURES

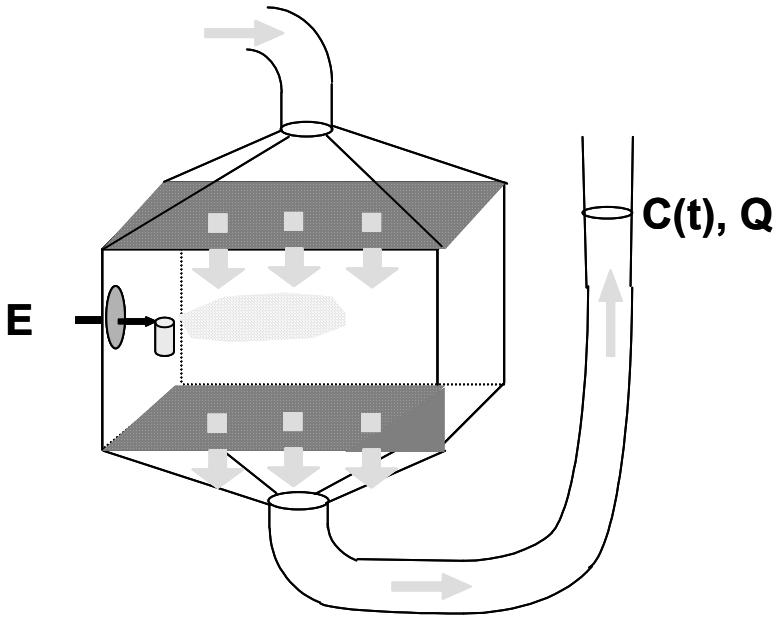


Figure 1. Schematic view of the ventilated chamber .

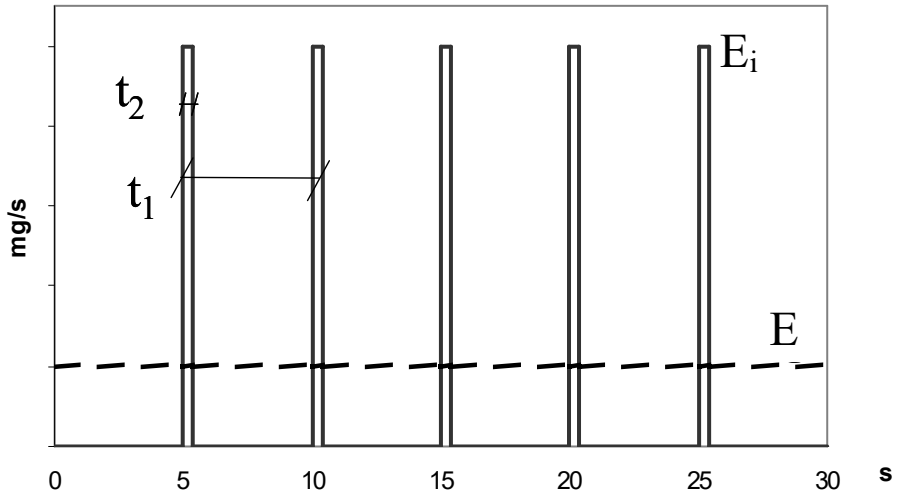


Figure 2. Effective and measured spray emission .

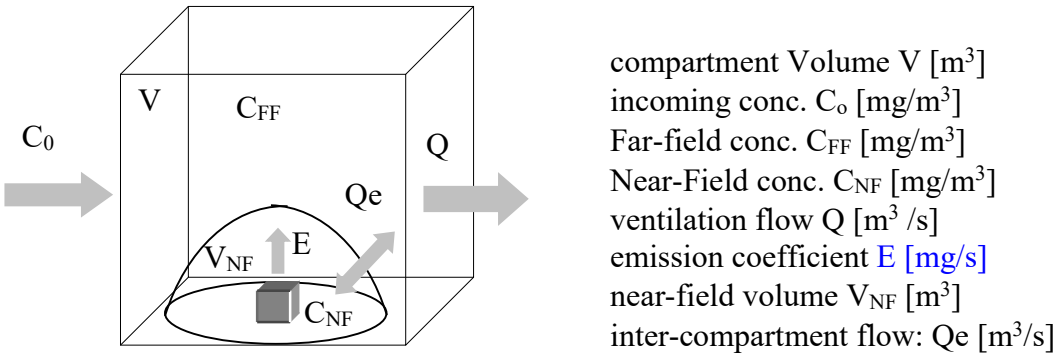
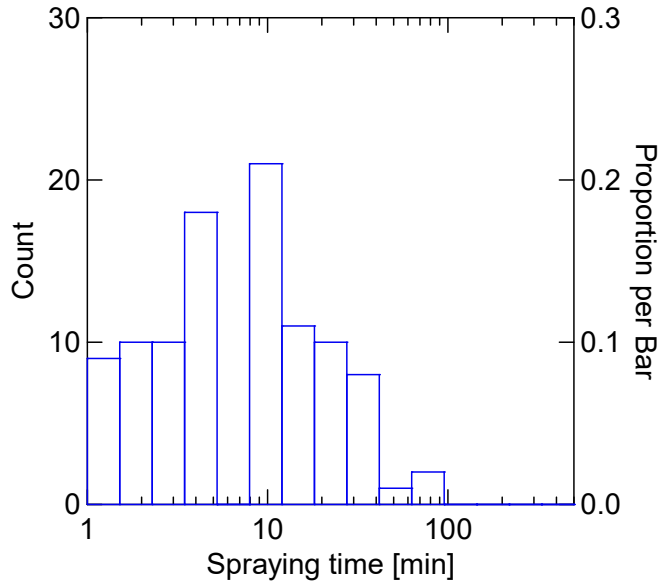
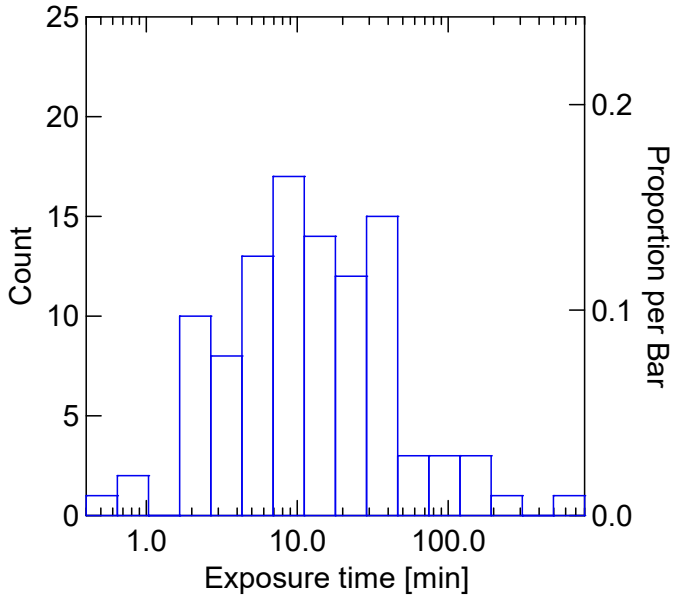


Figure 3. Schematic view of the two compartment model surrounding a punctual emission source (the grey cube).



(a)



(b)

Figure 4. Distribution of the reported exposure time: (a) spraying time, (b) total exposure time in the reported cases. The number of corresponding cases is given by y-axis (count)

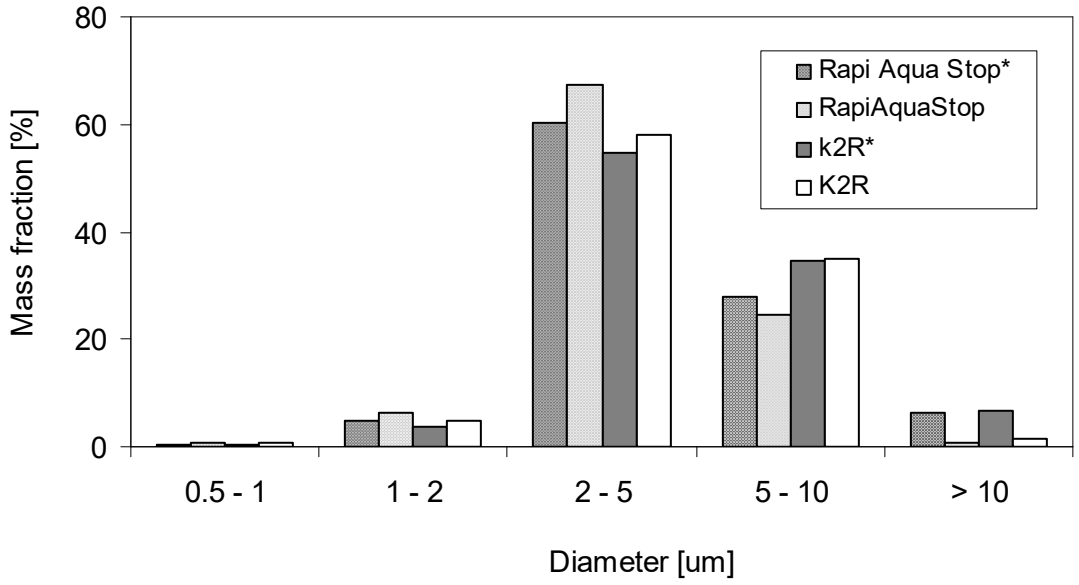


Figure 5. Example of particle size distribution obtained during spraying tests (*products involved in the toxicity outbreak as compared to similar non-toxic products)

Ventilation conditions	**Qe** (m^3/s)	**Air Renewal** (1/h)
indoor without ventilation	0.14	1
indoor with ventilation	0.20	2
location open on the outside	0.26	3
outdoor	0.32	-

Table 1. Implementation values for simulation.

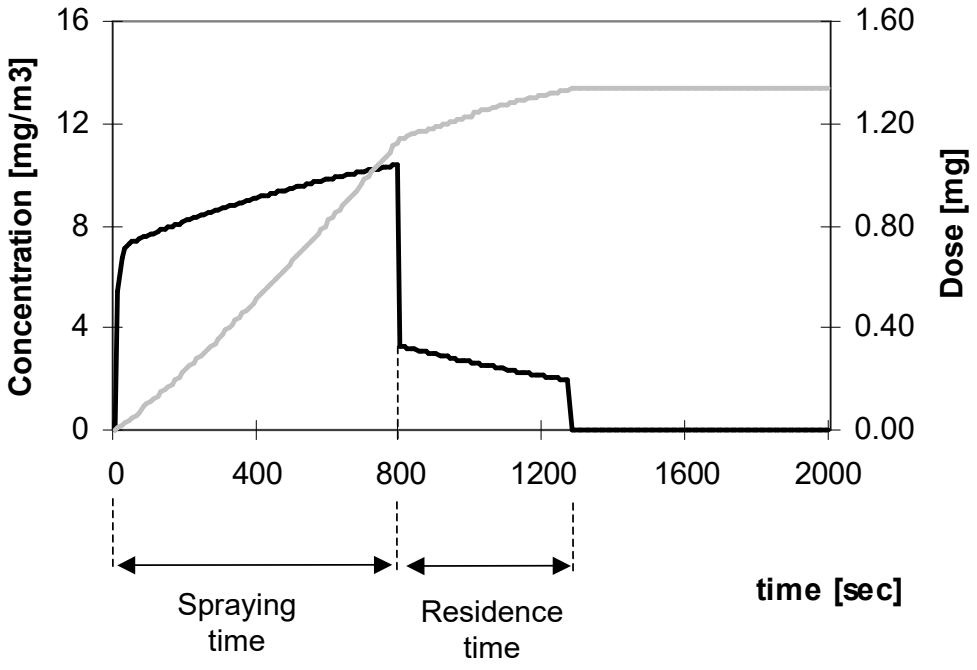


Figure 6. Typical concentration and dose profile

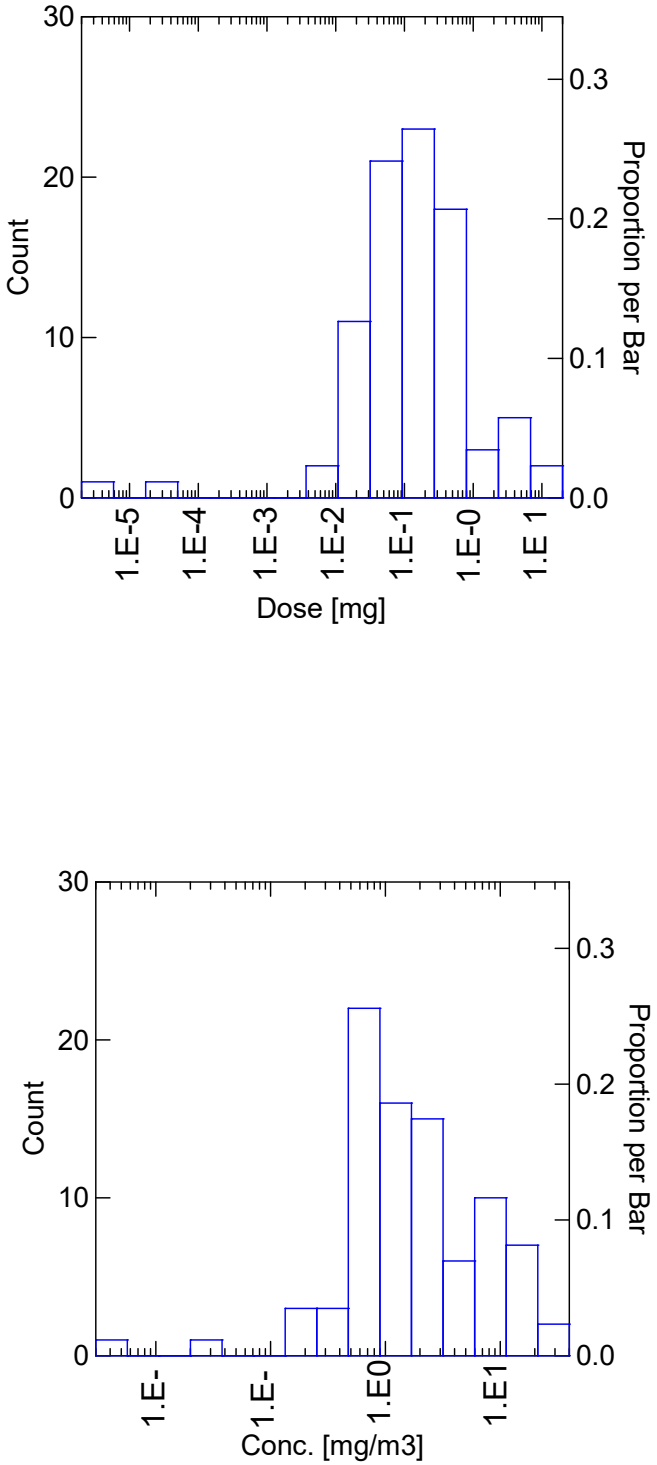


Figure 7. Assessed doses and maximal concentrations expressed in [mg] and [mg/m^3] of respirable aerosols

Spearman Correlation Coefficients (Prob>|r| under H0: Rho=0)

	Dose	Cmax	Spraying Time	Amount of Product
DELAY	-0.151 (0.328)	-0.175 (0.255)	-0.103 (0.475)	0.107 (0.476)
DYSP.	0.175 (0.373)	0.261 (0.179)	0.139 (0.448)	0.037 (0.848)
SCORE	0.216 (0.059)	0.159 (0.168)	**0.255 (0.014)**	**0.288 (0.009)**

Table 2. Perceived severity vs. exposure conditions

Correlation Coefficients (Prob>|r| under H0: Rho=0)

	Dose	Cmax	Spraying Time	Amount of Product
WBC*	0.328 (0.102)	**0.404 (0.040)**	0.079 (0.696)	-0.162 (0.439)
CRP*	0.075 (0.699)	**0.375 (0.045)**	-0.140 (0.445)	-0.017 (0.928)
PO2**	0.021 (0.927)	0.018 (0.938)	**0.440 (0.031)**	0.389 (0.074)

* = Spearman * *= Pearson

Table 3. Correlations between exposure conditions and clinical indicators

			Mean	p-value
Dose	smoking	yes no	0.51 0.80	0.37
	allergy	yes no	0.26 0.55	0.74
	asthma, COPD	yes no	0.12 0.50	0.32
Cmax	smoking	yes no	4.39 4.13	0.13
	allergy	yes no	2.65 4.53	0.79
	asthma, COPD	yes no	1.75 4.25	0.07
Spraying Time	smoking	yes no	11.26 12.55	0.49
	allergy	yes no	9.87 12.07	0.84
	asthma, COPD	yes no	12.78 10.81	0.45

Table 4. Comparisons between subgroups for smoking habits, asthma or COPD, and allergies

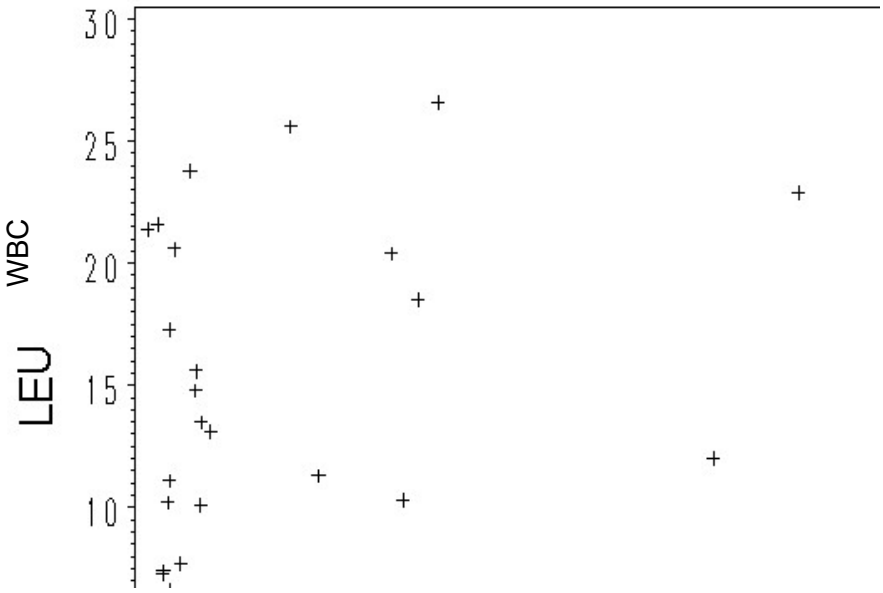


Figure 8. Relationship between Cmax and indirect inflammatory markers with WBC

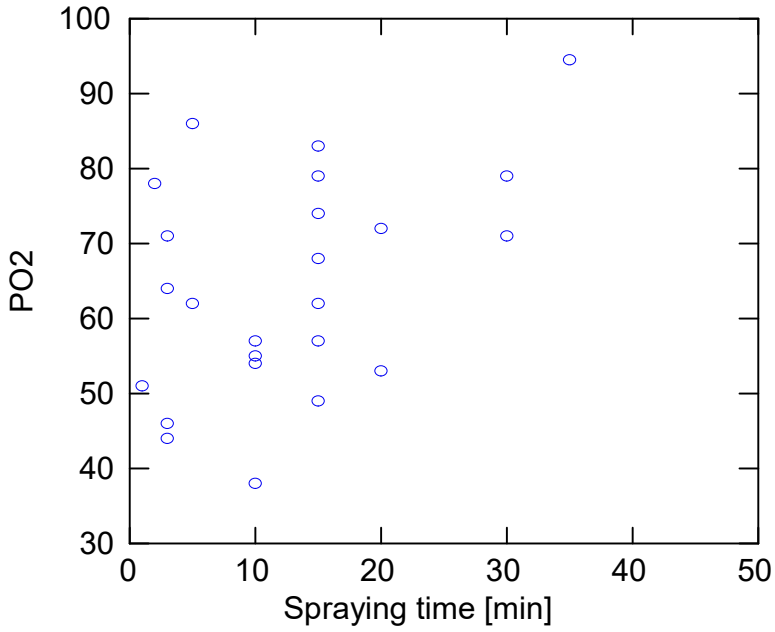


Figure 9. Relationship between PO_2 and spraying time