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EXPERT REPORT

evaluating the action mechanisms of

WESSO® AIR Med

to safeguard air-hygienic surroundings
in conjunction with the deactivation of all germs involved and elimination of pathogenic and antibiotic-resistant microorganisms

prepared by

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Preamble

The product

WESSO® AIR Med,

specifically developed on the basis of the starting formulation of the product

WESSOCLEAN® Lufthygiene – AIR Typ 2

of WESSOCLEAN® Wasserhygiene GmbH

to meet the hygiene requirements in critical clinical situations of treatment,

has been evaluated from the aspect of its mechanisms of action by Dr. med. Wolfgang Stengel for the Department of Research and Development in the field of Air Hygiene (FE LH) of WESSO AG under the direction of Dr. h. c. Heimo Jörg Wessollek in May 2006, taking the studies and expert opinions in hand as a basis.

This expert report is a summary of the relevant studies on the product included in the list of references, of experience gained in its clinical use and the discussions on this matter based on the current medical knowledge. The expert report deals with the following points:

- Ultrasonic cold nebulizing to apply the active substance
- Bacteriological examinations
- Risk-versus-benefit assessment in medical applications

- Experience gained in its clinical-medical application, in particular in intensive care units
- Action of components on cellular level

The Action Mechanisms of WESSO® AIR Med

1. Background: Procedure to improve the air-hygienic surroundings (conditioning) in the industrial sector

Nebulizing the product as an aerosol with a drop size of less than 5 µm of diameter using appropriate ultrasonic cold nebulizers represents a TÜV-certified procedure to improve the air and surroundings hygiene in particular in the area of industrial production by supporting well-introduced hygiene measures (TÜV study on the use of the product WESSOGREEN® AIR Type 2, 2004; Certificate, 2005). The use in connection with food manufacturing and processing aims at reducing and eliminating air germs (bacteria and their spores, mould fungi spores and yeasts) that may contaminate foods and, by germinating, diminish their quality (freshness) and cause their early microbial spoilage, including the formation of toxins harmful to health (e.g. aflatoxins formed by mould fungi, Staphylococcus toxins, botulin). By ultrasonic cold nebulizing a suspensible mist of very fine aerosol particles is produced that can wet suspended dust particles of bacteria and fungal spores, exposing them to the active substances contained in the aerosol drops. These are able to kill vegetative forms of bacteria and to prevent the forms of spores of bacteria and fungi from germinating, before they can contaminate unpacked or still unprocessed foods. Depending on the microbiological air pollution, 0.04 to 0.1 ml/m^3 of WESSOGREEN® AIR Type 2 are applied. According to the amount of active substances used in the production, this corresponds, by calculation, to 0.35 mg of active substances per m^3 of air. From samplings performed with the aid of the air germ collector HYCON RCS Plus of Biotest over a period of one year before and after the proper application, a germ-reducing effect on the air-carried germs in the order of magnitude of approximately 10^{-2} could be derived (TÜV study on the use of the product WESSOGREEN® AIR Type 2, 2004). These results have been confirmed by a great number of air germ measurements accompanying the application in the food industry. In milk-processing companies an extension of the minimum shelf life from 35 to 45 days has been achieved in yoghurt filling, without any detectable residues of the active substances of WESSOGREEN® AIR Type 2 remaining on the product (Analysis and Assessment

considering the Law relating to Food and Drugs, Technologisches Beratungs- und Entwicklungslabor H.-J. Iben, 2003[1]).

2. Use of an advanced product, hereinafter referred to as WESSO® AIR Med, in critical medical-clinical circumstances of treatment concerning the hygiene requirements

Against the background of the convincing results in this sphere, there has grown an interest in a procedure just effective as that to be applied in critical medical-clinical circumstances of treatment concerning the hygiene requirements, that is able to influence the hygienic situation of the air and room surroundings favorably, improving thus the conditions required to achieve the goal of treatment.

2.1. Tests in the Intensive Care Unit of the Euromed Klinik Fürth and in the MRSA Isolation Unit of the Intensive Care Clinic of Nürnberg-Schwaig

Thus, WESSO® AIR Med has been used for four years in the Intensive Care Clinic of Nürnberg-Schwaig and in the Intensive Care Unit of the Euromed Klinik Fürth in connection with the treatment of patients with germ colonization (decolonization) by methicillin-resistant Staphylococci (MRSA), in a modified form with nebulization at intervals. These are seriously traumatized patients with skull-brain injuries, partly still without consciousness, but with spontaneous, not machine-supported breathing (with tracheotomy), partly in the waking state and therefore increasingly approachable to rehabilitation measures such as physical therapy. MRSA colonization (hospital germs), in particular in the nasal part of pharynx and on the skin, is to be put down to a former stay in clinics with acute care. It represents a high risk of hospital infections, in particular of pneumonia, accompanied in such patients by a high rate of serious complications. Patients with MRSA colonization are admitted to an isolation unit, where, under the strictest hygienic precautions, the decolonization measures recommended by the Robert Koch Institute are carried out, such as administration of an antibiotic-containing nasal ointment and antiseptic whole-body washings.

[1] Technological Advisory and Development Laboratory H.-H. Iben, 2003

2.2. Importance of the Application within the Scope of the MRSA Risk Management (Decolonization)

It is recommended that in situations of breakout also such personnel suffering from germ colonization, proven by smears, shall be subjected to these quite stressful measures and exempted from their duties until they are provably free from germs. This, and the personnel-intensive care in intensive isolation units, may cause bottlenecks in the availability of personnel. In connection with the tense financial situation of clinics, this has induced some of them to reject the hospitalization of patients with MRSA colonization. This problem is increasingly recognized by the occupational groups concerned, and also by a broad public, particularly as there are clear differences also between various countries within Europe (Kipp F et al., 2004; Stolze C, 2005).

Even though the risk of germs to be transmitted by direct contact is predominant, discussions - according to the current knowledge - on a transmission by air (airborne) are going on, also on a "droplet infection" with the patient suffering at the same time from a viral infection of the upper respiratory tract (Kappstein I, 2004). The contamination of surfaces in the surroundings of colonized patients is a reservoir to contaminate, for example, the hands or work gloves of the medical personnel (Boyce et al., 1997). So there is also the wish to take additionally care of low-germ treatment surroundings including the respiratory air (in case of patients with tracheotomy). Although the procedure brings about primarily a reduction of the air germs, apart from that a general decrease of germs, especially on surfaces (but not a "disinfection of surfaces"), quite certainly represents an effect in the longer term. This is shown by the number of air germs diminishing in the course of the first weeks of continuous application. In special clinical situations of treatment, a substance-bound procedure for air germ reduction with a component of short-time action in the fore and an additional component of continuous action could turn out to be more advantageous than a physical procedure (middle ultraviolet light, laminar airflow) - to be more practicable in a still greater number of treatment situations. The resistance of bacteria to the product substances hydrogen peroxide, sodium benzoate and sorbic acid - unlike all antibiotics and also chemotherapeutic agents introduced - is not known. The application does not increase the selection pressure on the bacterial population and the occurrence of bacterial strains resistant to an even greater number of agents.

The use of WESSO® AIR Med in MRSA isolation units as a preventive measure against the transmission of pathogenic microorganisms and diseases also aims at preventing the personnel from germ colonization who - as has been proved - can turn into transmitters as well. In outpatient care, similar conditions in germ reduction of the air and treatment surroundings can be given, for example in the case of stoma (artificial anus) and chronic wounds, e.g. of diabetics, where WESSO® AIR Med has also been tested as an agent used to reduce additionally the danger of infection and to prevent infections.

2.3. Surveys during the use at a MRSA unit: Determination of the number of air germs with germ differentiation (antibiogram) and simultaneous documentation of clinical findings and therapeutic measures

Recently a series of detailed air germ measurements has been carried out at the isolation unit of the Intensive Care Clinic of Nürnberg-Schwaig prior to the application and after four weeks of continuous application (in one-hour periods with one-hour treatment-free intervals), accompanied by the documentation of all other diagnostic measures, including microbiological examinations, and the antimicrobial treatment. The results (not yet published) show in an impressive manner the complete disappearance of MRSA on air germ sedimentation plates and in the measurement of air germs carried out by means of an air germ collector, a special centrifuge, also in the corridor frequented only by the personnel, where, prior to the application of the product, MRSA had been detected at five of eight sampling points. The total number of germs, determined with an air germ collector made by Biotest, decreased significantly to 26 % of the initial level ($P < 0.01$).

2.4. Risk-versus-benefit assessment of an additional therapeutic measure supporting the clinical therapy and preventing infections

2.4.1. Considering the goal of the treatment

An important aspect of a comprehensive risk-versus-benefit assessment of the procedure is the seriousness of the disease, the treatment of which shall be supported.

The challenges to be faced by a therapy of MRSA infections have been described in a short summary to the essay "Methicillin-resistant Staphylococci. Appearing in old people's homes as frequently as in hospitals" (Neuhaus B, 2003) as follows:

"Profile of an unpleasant germ: Staphylococcus aureus as well as methicillin-resistant Staphylococci (MRSA) colonize the skin and mucous membrane of healthy people, above all the nasal vestibule. From here, the germs can spread to the throat, the intestines, the hands and so on. If immunocompromised people are affected, S. aureus as well as MRSA may cause serious infections such as wound infections, pneumonia or sepsis – with the difference that it is much more difficult to treat MRSA because of its antibiotic resistance. On the one hand, only few preparations are usable for the treatment, on the other hand, these preparations can be applied only to a limited extent due to their possible side-effects or due to the resistance development on their part."

The medical staff concerned that is nursing and treating the patients has to bear the responsibility not to transmit unintentionally pathogenic microorganisms, possibly even constitute a "reservoir". In the case of a proved germ colonization (in breakout situations) they must be exempted from their duty temporarily in order to undergo decolonization measures until the absence of germs is proved, with all strains involved, also strains of psychical nature.

2.4.2. Findings on the effects of the components with regard to the risk-versus-benefit assessment

Introduction and certification of the application of this formulation has been accompanied by toxicological expert opinions (expert opinion of Prof. Dr. Heeschen and Prof. Dr. Gräf) and medical examinations of healthy employees according to occupational safety regulations (study and expert opinion by Dr. Jahn). With regard to sorbic acid and sodium benzoate, model calculations have furnished proof of the fact that, when continuously applying the highest recommended dosage of the product, i.e. 0.1 ml/m^3/h, in the course of one work day, the acceptable daily intake (ADI value) of 5 mg/kg of body weight or 25 mg/kg of body weight cannot be exceeded in the employed persons due to a high safety factor (15 and 73, respectively) (Expert Opinion - Hygienic-Toxicological Assessment, Prof. Dr. Heeschen).

Additional photometrical determinations of the hydrogen peroxide concentration in the room air yielded values below 1.0 mg/m^3 even when applying the triple of the highest recommended dosage. These values were clearly below the value of the maximum allowable concentration of 1.4 mg/m^3 (Determination of the Concentration of Hydrogen Peroxide in the Room Air, Chemisches Laboratorium Dr. Weßling GmbH, 2005). This can be explained also by the fact that a considerable part of the hydrogen peroxide contained in the product decomposes to water and oxygen as a result of the energy input by applying the product by ultrasonic nebulizing. Concerning the application in rooms occupied by patients it must be taken into account that, up to now, a maximum of 25% of the highest recommended dosage has been applied over longer periods of days and weeks that have been well tolerated by patients and personnel. Within the period of experience of four years with repeated targeted application in intensive care units of two clinics with altogether approximately 60 beds, physicians of these clinics investigated in three cases the question of a connection between different symptoms such as erythemas appearing in nursing personnel and the application of WESSO® AIR Med by allergy tests (Prick Test) and, in addition to that, by substituting temporarily a physiological salt solution for WESSO® AIR Med without informing the nursing personnel thereof. There was no indication of any allergy to the components. It should be noted that a (pseudo)allergic reaction to benzoic acid with a cross-reaction to salicylates has been described in the literature. However, actually only 88 µg/m^3/h of sodium benzoate are applied by nebulization - a substance that can be found frequently in the nature, also as a natural component of foodstuffs such as fruits (plums, cranberries, strawberries). Due to its structure similar to that of an unsaturated fatty acid, sorbic acid is considered to be absolutely not harmful to the health of humans (quick transformation in metabolism).

2.5. Further Development of the WESSO® AIR Med Production Method and its Application Technology

If a product is used to enhance the medical treatment in clinics, special demands are made on testing the appropriate dosage, monitoring and documenting the amount of active substances applied and, in the production process, on the quality and purity of the raw material, including the water used, as well as on the continuous quality assurance process (quality control). This will be taken into account by the product's admission as a medical product that is expected soon (CE marking), as well as with an ultrasonic cold nebulizing

system currently being tested that allows the applied quantity (volume or weight) to be controlled electronically according to the presetting.

3. Components and Action Mechanisms

The production of WESSO® AIR Med has been standardized, as own experiments and examinations within the scope of quality assurance showed that the effectiveness cannot be explained by the sum of its individual components, but only by the special production method and the synergistic effects of the components properly matched to one another. This has been documented in the literature referred to below.

As components with antimicrobial effect, the aqueous solution of WESSO® AIR Med contains the sodium salt of the benzoic acid (sodium benzoate) and sorbic acid, each in clearly lower concentrations than those habitually present when using these substances as food additives. Both substances can be described as being "identical to nature": Benzoic acid is found in higher concentrations in various fruits such as cranberries, plums, and strawberries; sorbic acid is found for example in rowanberries.

Benzoic acid (C_6H_5COOH, E 210) and its salts (sodium benzoate: E 211), originally introduced as a substitute for the salicylic acid, closely related in structure, intervenes in several ways in the enzyme activity of the microorganism cell: The anaerobic fermentation of glucose by phosphofructokinase is inhibited by 95 % (Krebs et al., 1983), also enzymes that regulate the oxidative phosphorylation, the acetic acid metabolism, as well as the citric acid cycle (Bosund, 1962). Apart from that, the function of the cell wall is influenced, and, by lowering the intracellular pH value, the regulation of the acid-base balance of the microbial cell is disturbed (Salmond et al., 1984). The action of the benzoic acid is more directed against yeasts and mould fungi than against bacteria such as clostridia. In the literature, mainly minimal inhibitory concentrations between 200 and 5 000 ppm, depending on the microbial species and the pH value, are indicated. - In the human organism, benzoic acid, after good absorption through the intestine, is transformed in the liver with the amino acid glycine to hippuric acid and quickly excreted through the kidney. The quick transformation by human metabolism is the reason for the application safety (WHO Food Additive Series No. 18, 2005; WHO CICA document no. 26, 2000).

Sorbic acid, from its structure to be regarded as a di-unsaturated fatty acid (trans,trans-2,4-hexadienoic acid, $C_6H_8O_2$, E 200), was introduced as a food additive (preservative) only after 1950 and was examined thoroughly. Similar to benzoic acid, a greater number of enzymes of the microbial cell is discussed as a point of action of the sorbic acid, in particular enzymes of the carbohydrate metabolism and the citric acid cycle (Rehm, 1967). Due to its double bonds, sorbic acid enters into covalent bonds with SH groups of enzymes, deactivating them that way (Martoadiprawito and Whitaker, 1963). Also the catalase and peroxidase of mould fungi are inhibited (Lück, 1957). The cell wall shall be an additional point of action, which changes the permeability to ions and, apart from that, inhibits also the growth by influencing the transport of building blocks like amino acids, e.g. of Escherichia coli (Eklund, 1985). The range of action includes yeasts and mould fungi. In addition to that, catalase-positive bacteria are inhibited to a greater extent than catalase-negative ones. Combining sorbic acid with low concentrations of other preservative substances, it clearly inhibits also clostridia (Ivey et al., 1978). The minimal inhibitory concentrations are between 100 and 10 000 ppm, depending on the microbial species and the pH value.

The combination of benzoic acid and sorbic acid has proved to be favorable, because bacteria, not influenced by the individual substances, are included in the range of action (Rehm and Stahl, 1960). A real resistance development, i.e. increase of the minimal inhibitory concentration in applying subthreshold concentrations of sorbic acid or benzoic acid, is not known. Interesting enough, sorbic acid inhibits the formation of aflatoxin still more than the growth of mould fungi, so it seems to be appropriate in a special way for the prophylaxis of food poisonings (Bullermann, 1983). The application safety of sorbic acid is based, on the one hand, on the obviously higher sensitivity of enzymes in microorganisms, as, for example, the alcohol dehydrogenase, compared with enzymes in the human organism, as well as on the quick and complete decomposition in humans - mainly by ß-oxidation, as taking place in fatty acids (WHO Food Additive Series No. 5, 1974; Walker, 1990).

In the production process also hydrogen peroxide (H_2O_2) is used. It has turned out that the greatest part of this substance of low stability that also decomposes rapidly to water and oxygen when being warmed or in the presence of organic material, is removed by the energy input in the process of ultrasonic cold nebulization (piezoelectric procedure). That is why the respective value of the maximum allowable concentration (MAC value) is not exceeded in the

photometric determination, even not if the triple of the highest recommended dosage of 0.1 ml of the product per m^3 of air will be applied (Determination of the Concentration of Hydrogen Peroxide in the Room Air, Chemisches Laboratorium Dr. Weßling GmbH, 2005). - With regard to sodium benzoate and sorbic acid, model calculations have furnished proof of the fact that, when continuously applying the product in food-processing companies in the course of one work day, the acceptable daily intake (ADI value) of 5 mg/kg of body weight or 25 mg/kg of body weight cannot not be exceeded in the employed persons due to the high safety factor (15 and 73, respectively) (Expert Opinion - Hygienic-Toxicological Assessment, Prof. Dr. Heeschen).

4. Microbiological Examinations

The bactericidal effectivity of the finished solution can be assessed on the basis of an expert opinion prepared at the Institute of Medical Hygiene of the Erlangen-Nuremberg University on a product for applications in the field of drinking-water hygiene, which has a comparable material composition. It refers to a study done in conformity with the Directives of the German Society for Hygiene and Microbiology, including Gram-positive as well as Gram-negative bacteria that play an important role as pathogenic or indicator germs (Escherichia coli, Staphylococcus aureus, Streptococcus faecalis, Mycobacterium tuberculosis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Proteus mirabilis, Clostridium sporogenes, Salmonella typhi), also the yeast Candida albicans. According to that it can be expected that by wetting with a 2.5 % aqueous solution of WESSO® AIR Med the above-mentioned germs will die within five minutes, with little variability in their sensitivity. The relationship between yeasts and mould fungi, as well as the experience acquired through a great number of observational cohort studies suggest that mould fungus species, such as Aspergillus niger, have an equally pronounced sensitivity to WESSO® AIR Med. In further tests and expert opinions, reproduction-inhibiting up to bactericidal properties of the diluted product acting on Legionella pneumophila and a multiresistant Staphylococcus aureus strain have been demonstrated, with times of exposure from 5 to 30 minutes (expert Opinion of Prof. Dr. Dr. Gräf, 2002).

5. Summarized Assessment

Based on all examination results obtained, expert opinions, the literature contained in the list of references, and observational cohort studies, it can be stated that the product

WESSO® AIR Med

intended to safeguard air-hygienic surroundings in conjunction with medical measures

- is well-tolerated by humans and, under toxicological aspects, harmless to people;

- is, under ecological aspects, not objectionable;

- achieves, under microbiological aspects, an active reduction of germs, including the pathogenic troublesome germs (MRSA, Legionella) without implying the risk of a resistance development;

- applied in critical clinical situations of treatment with special requirements as to hygienic measures, reduces the germ load of the room air and leads to a general reduction of the level of germ load in the room – acting as an agent for preventing risk factors (colonization) and infectious diseases or supporting their treatment.

Erlangen, May 2006

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[1] The German titles have been translated for information purposes only (the translator)

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