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(54) Abstract Title
Detection of analyte species

(57) The analyte is separated from a sample by a selective selection means 3 which is defined as including an immunological species (e.g. an antibody) which is capable of taking part in an immunological specific binding reaction with an analyte species selectively to separate the analyte species from the sample, and/or includes an imprinted material (such as a molecularly imprinted material) of a type which is capable of undergoing selective interaction with the analyte species selectively to separate the analyte species from the sample. The separated species is detected by "chemical sensor means" 5 which is defined as a suitable transducer associated with a material capable of interacting with an analyte species, or an infrared detector. One or more species may be separated by the selective selection means and the sensor may detect one or a plurality of species. Examples of suitable separating means and chemical detectors are given.

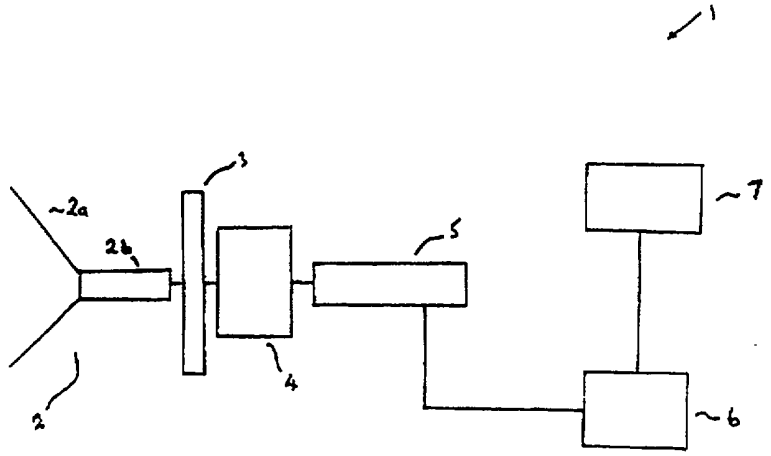

Fig 1.

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Detection

The present invention relates to apparatus suitable for use in the detection of analyte species and to a method of detection suitable for use in the detection of analyte species.

According to one aspect of the present invention there is provided apparatus, suitable for use in the detection of analyte species, which apparatus includes a selective separation means (as hereinafter defined), for separation of an analyte species from a sample, and sensor means, comprising a chemical sensor means (as hereinafter defined), for detecting analyte species received from the selective separation means.

According to another aspect of the present invention there is provided a method, which method is suitable for use in the detection of analyte species, which method includes separating an analyte species, if present, from a sample by use of a selective separation means (as hereinafter defined), and detecting the analyte species, if present, by use of a sensor means, comprising a chemical sensor means (as hereinafter defined), for detecting analyte species received from the selective separation means.

A selective separation means in accordance with the present invention includes an immunological species (e.g. an antibody) of a type which is capable of taking part in an immunological specific binding reaction with an analyte species selectively to separate the analyte species from the sample, and/or includes an imprinted material (such as a molecularly imprinted material) of a type which is capable of undergoing selective interaction with the analyte species selectively to separate the analyte species from the sample.

Unless otherwise indicated, "immunological species" in this Specification means a species of a type which is capable of taking part in an immunological specific binding reaction with an analyte species to separate the analyte species from the sample.

Where, for example, as is further disclosed hereinafter, the present invention is applied to the detection of more than one type of analyte species in a sample, a selective separation means in accordance with the present invention may include a plurality of different types of immunological species, or include a plurality of different types of imprinted material, or may include any suitable combination of one type of immunological species or a plurality of types of immunological species and one type of imprinted material or a plurality of different types of imprinted material which may selectively separate an analyte species or a plurality of analyte species from a sample.

Thus, by way of example, a selective separation means in accordance with the present invention may include a plurality of different types of antibody, or include a plurality of different types of imprinted material, or may include any suitable combination of one type of antibody or a plurality of types of antibody and one type of imprinted material or a plurality of different types of imprinted material which may selectively separate an analyte species or a plurality of analyte species from a sample.

For example, a selective separation means may include one type of immunological species, or may include a plurality of types of immunological species, or may include one type of imprinted material, or may include a plurality of types of imprinted materials, or may include one type of immunological species and one type of imprinted material, or one type of immunological species and a plurality of types of imprinted material, or may include a plurality of types of immunological species and

one type of imprinted material, or may include a plurality of types of immunological species and a plurality of types of imprinted material.

Thus, for example, a selective separation means may include one type of antibody, or may include a plurality of types of antibody, or may include one type of imprinted material, or may include a plurality of types of imprinted materials, or may include one type of antibody and one type of imprinted material, or one type of antibody and a plurality of types of imprinted material, or may include a plurality of types of antibody and one type imprinted material, or may include a plurality of types of antibodies and a plurality of types of imprinted materials.

By way of example, an immunological species capable of taking part in an immunological specific binding reaction with an analyte may be an antibody of a type which is capable of undergoing specific binding with an analyte species or an antigenic ligand (such as an antigen or a hapten) capable of being specifically bound by a corresponding antibody.

Where an immunological species is used to effect separation, or where a plurality of types of immunological species are used to effect separation, the selective separation means may be considered to be a selective biological separation means.

Thus, for example, where an antibody of a given type is used to effect separation, or where a plurality of antibodies of given types are used to effect separation, the selective separation means may be considered to be a selective biological separation means.

In view of the foregoing disclosure, it will be appreciated that a selective separation means may include one type or a plurality of types of selective separation species and it is to be appreciated that a selective separation species may be an immunological species (e.g. an antibody) or an imprinted material.

The present invention may offer, for example, the advantages of "two-tier" selectivity (i.e. selective separation means and chemical sensor means), rapid response (e.g. in near real-time), reversibility of sensor response and convenient system recovery.

The use of immunological species (e.g. antibodies) and/or imprinted materials alone as a basis of detection of analyte species may suffer from the disadvantage that immunological species (e.g. antibodies) and imprinted materials may be difficult to configure to give a conveniently fast (e.g. a real-time) response and from the disadvantage that conveniently rapid reversibility of binding or interaction with an analyte species may not be attainable.

The use of a chemical sensor or chemical sensors alone as a basis of detection of analyte species may suffer from the disadvantage that a desired high selectivity may not be obtainable and also from the disadvantage that a desired degree of sensitivity may not be attainable.

In accordance with the present invention the selective separation means may be used, for example, to give high selectivity, a concentration means (as further disclosed hereinafter) may be used, for example, to facilitate high sensitivity, and the chemical sensor means may be used, for example, to give near real-time response, reversibility of response and further selectivity.

Thus, the present invention may be utilised substantially to overcome disadvantages which may be encountered with other types of detection.

A chemical sensor means, in accordance with the present invention, comprises a suitable transducer associated with a material capable of interacting with an analyte species, or comprises an infrared detector; the material capable of interacting with an analyte species

may be provided, for example, as a coating or a film on a surface of a transducer.

The material capable of interacting with an analyte species may be, for example, such as to be capable of interacting non-selectively with an analyte species (i.e. may be a non-specific or non-selective material) or may be such as to be capable of interacting selectively with an analyte species (i.e. may be a selective material).

Thus, for example, the material capable of interacting with an analyte species may be a material (e.g. a polymer) capable of non-selective sorption (absorption or adsorption, or a combination of these), or the material capable of interacting with an analyte species may be a material (e.g. an imprinted material) capable of selective sorption (absorption, or adsorption, or a combination of these); by way of example, if desired, a combination of non-selective material or non-selective materials and a selective material or selective materials may be utilised.

Thus, by way of example, a chemical sensor means in accordance with the present invention may have a surface which is coated with a material which is selective, for example specific (e.g. highly specific), with regard to analyte species it is desired to detect.

Thus, by way of example, a sensor surface may have a coating deposited as a thin film thereon. Thus, for example, a sensor for use in accordance with the present invention, may comprise an acoustic wave device having a surface which has a coating deposited as a thin film.

By way of example, any suitable coating may be used in accordance with the present invention; examples of materials which may be used as coatings include functionalised polymers, receptors, molecularly-imprinted materials and organometallic species.

The chemical sensor means may be, for example, a piezoelectric sensor (e.g. an acoustic-electric transducer device, examples of which are a surface

acoustic wave device (SAW) or any other acoustic wave transducer as is disclosed hereinafter) associated with a material capable of interacting with an analyte species, a metal oxide sensor (e.g. a metal oxide semiconductor sensor), a conducting polymer sensor, an optical chemical sensor associated with a material capable of interacting with an analyte species, or a catalytic sensor (e.g. a pellistor).

By way of example, a chemical sensor comprising an olfactory sensor array may be used in accordance with the present invention.

It will be appreciated that the type of chemical sensor means used may be chosen on the basis of its suitability for a given application.

A chemical sensor means may be used, as appropriate, in connection with the detection of one type of analyte species or the detection of a plurality of different types of analyte species.

Where the present invention is to be utilised in seeking to detect the presence or absence of an analyte species which it is thought may be present in a sample at an inconveniently low level (e.g. at a level which renders detection difficult or impossible by use of known apparatus or methods) the apparatus in accordance with the present invention preferably includes a concentration means and a method in accordance with the present invention preferably includes a concentration step.

Thus, in accordance with one embodiment of the present invention, there is provided apparatus, which is suitable for use in the detection of an analyte species, which apparatus includes a selective separation means for separation of an analyte species from a sample, means for concentrating analyte species separated from the sample, and sensor means, comprising a chemical sensor means, for detecting analyte species received from the selective separation means via the means for concentrating analyte species.

In accordance with another embodiment of the present invention there is provided a method, suitable for use in the detection of an analyte species, which method includes separating an analyte species, if present, from a sample by use of a selective separation means, concentrating any such separated analyte species and detecting the analyte species, if present, by use of a sensor means, comprising a chemical sensor means, for detecting the analyte species received from the selective separation means via a concentrating step.

By way of example, if desired, a concentration means may be part of a selective separation means.

Where, for example, a single type of analyte species is to be detected in accordance with the present invention, the chemical sensor means may be, for example, a single discrete chemical sensor which is capable of responding to, and thereby detecting the presence of, a single type of analyte species (e.g. a single type of chemical species).

Thus, for example, a single type of analyte species may be separated from a sample by means of a selective separation means which includes one type of immunological species (e.g. antibody), or one type of imprinted material, said immunological species (e.g. antibody) being of a type which is capable of taking part in an immunological specific binding reaction with the analyte species, or said imprinted material being of a type which can undergo selective interaction with the analyte species, and said analyte species may then be transferred (after any further processing, if required, as hereinafter disclosed) to a single chemical sensor means which is substantially specific for the analyte species.

By way of example, a single chemical sensor means may be any suitable chemical sensor, in accordance with the present invention; thus, for example, a single chemical sensor means may be a suitable piezoelectric sensor (e.g. an acoustic-electric transducer device (such

as a surface acoustic wave device (SAW) or any other acoustic wave transducer as is disclosed hereinafter) associated with a material capable of interacting with an analyte species, a metal oxide sensor (e.g. a metal oxide semiconductor sensor), a conducting polymer sensor, or an optical chemical sensor associated with a material capable of interacting with an analyte species, or a catalytic sensor (e.g. a pellistor).

In view of the foregoing disclosure it will be appreciated that where, for example, a single type of analyte species is to be detected in accordance with the present invention, the chemical sensor means may be, for example, such that it responds substantially only to a given analyte species; thus, for example, a discrete chemical sensor means may be substantially specific with respect to a given analyte species.

(A chemical sensor may be considered, for example, to be specific for a given analyte species if the sensor responds substantially only to that analyte species and not to other species.)

A chemical sensor may be considered, for example, to respond to a given analyte species if the chemical sensor gives a measurable signal (e.g. electrical signal (e.g. as a result of mass change) or an optical signal (e.g. a fluorescence signal)) as a result of a chemical interaction between the analyte species and the sensor.)

By way of example, a single type of analyte species may, optionally, be detected by use of a chemical sensor means which comprises an olfactory sensor array; said olfactory sensor array comprises a plurality of olfactory sensors.

An individual olfactory sensor of an olfactory sensor array may be non-specific with respect to a given type of analyte species but an olfactory sensor array may be such that it gives a pattern or profile of responses which is uniquely diagnostic of a given type of analyte species.

Thus, for example, each sensor in an olfactory sensor array may be such as to respond differently to a given analyte species such as to give a pattern or profile of responses which is uniquely diagnostic of a given analyte species.

From the foregoing disclosure it will be appreciated that although an individual olfactory sensor may be non-specific for a particular single analyte species (i.e. the olfactory sensor may be capable of responding to more than one type of analyte species though differently to each of said types of species) the use of an array of different olfactory sensors enables the pattern or profile of responses to be used in the detection of a specific single analyte species.

Although reference has hereinbefore been made to detecting a single type of analyte species, the present invention may also find application in, for example, the detection of more than one type of analyte species in a sample. Thus, for example, the present invention may be applied to detection of a plurality of different types of analyte species in a given sample.

Thus in accordance with a further embodiment of the present invention there is provided apparatus, suitable for use in the detection of analyte species, which apparatus includes a selective separation means, for separating each of a plurality of different types of analyte species from a sample, and a sensor means, comprising a chemical sensor means, said sensor means being appropriate for detection of a plurality of different types of analyte species obtained from a sample and received from the selective separation means.

According to yet a further embodiment of the present invention there is provided a method suitable for use in the detection of analyte species, which method includes separating a plurality of different types of analyte species, if present, from a sample using a selective separation means for separating each of a plurality of

different types of analyte species from a sample, and detecting each of the different types of analyte species, if present, by means of a sensor means comprising a chemical sensor means, said sensor means being appropriate for detecting a plurality of different types of analyte species obtained from a sample and received from the selective separation means.

A chemical sensor means suitable for use in the detection of a plurality of different types of analyte species may be, for example, a single discrete chemical sensor means which may be such as to be able to respond to more than one type of analyte species. Thus, for example, a single discrete chemical sensor means may be able to respond to, and thereby indicate the presence of, more than one type of analyte species and said plurality of different types of analyte species may be introduced separately and sequentially to the discrete chemical sensor means after being separated from the sample, and from each other, by the selective separation means.

Thus, for example, a first type of immunological species (e.g. antibody), or first type of imprinted material, may be used to separate a first type of analyte species and a second type of immunological species (e.g. antibody), or second type of imprinted material, may be used to separate a second type of analyte species from a sample and from each other and said first analyte species type may then be applied to the chemical sensor means, removed after detection, and then the second analyte species type may be applied to the chemical sensor means such that the first and second types of analyte species are detected separately by the same chemical sensor means.

By way of further example, a chemical sensor means suitable for the use in the detection of a plurality of different analyte species may be, for example, in the form of a plurality of discrete chemical sensor means, said plurality of discrete chemical sensor means being

appropriate for detection of a plurality of different types of analyte species obtained from a sample; thus, for example, a plurality of discrete chemical sensor means may be provided such that a first discrete chemical sensor means is appropriate for specifically detecting a first given type of analyte species, a second given discrete chemical sensor means is appropriate for specifically detecting a second given type of analyte species and so forth, the number of different discrete chemical sensor means in the plurality of discrete sensor means being dependent upon the number of different analyte species that it is desired to detect in a sample.

If desired, a plurality of discrete chemical sensor means may be used in the form of a panel of sensors.

Reference may be made to appropriate portions of the disclosure appearing hereinbefore with reference to examples of sensor means which may find application in accordance with the present invention.

By way of example, after separation of different types of analyte species using different types of immunological species (e.g. antibodies), or different types of imprinted materials, or any suitable combination of suitable immunological species (e.g. suitable antibody or antibodies) and imprinted material or imprinted materials, in the selective separation means, different types of analyte species may be applied to appropriate discrete chemical sensors such that each of the sensors is able to respond appropriately if an analyte species to which it is substantially specific is present.

By way of further example, a chemical sensor means suitable for use in the detection of a plurality of different analyte species may be, for example, a plurality of olfactory sensors, which together form an olfactory sensor array.

The plurality of olfactory sensors in such an array may be such that although each sensor in the plurality of sensors is, individually, non-specific for a given type

of analyte species, the plurality as a whole when used together as an array may be such that the array gives a pattern or profile of responses which is uniquely diagnostic of specific different analyte species. Thus, for example, a given plurality of such olfactory sensors may be used to detect the presence of a number of different types of analyte species, each of which different type of analyte species gives a different pattern of responses when applied to the array.

In view of the foregoing disclosure, it will be appreciated that, in accordance with a further embodiment of the present invention, there is provided apparatus, suitable for use in the detection of analyte species, which apparatus includes a selective separation means for separating a plurality of different types of analyte species from a sample, and a sensor means comprising a chemical sensor means which chemical sensor means comprises a plurality of sensors which plurality of sensors forms an olfactory sensor array, said sensor means being appropriate for the detection of a plurality of different types of analyte species obtained from a sample and received from the selective separation means.

Also from the foregoing disclosure it will be appreciated that, in accordance with a further embodiment of the present invention, there is provided a method suitable for use in the detection of an analyte species, which method includes separating a plurality of different types of analyte species, if present, from a sample using a selective separation means for separating each of a plurality of different types of analyte species from a sample, and detecting each of the different types of analyte species, if present, by means of a sensor means, comprising a chemical sensor means which chemical sensor means comprises a plurality of sensors which plurality of sensors forms an olfactory sensor array, said sensor means being appropriate for detection of a plurality of

different types of analyte species obtained from a sample and received from the selective separation means.

Furthermore, in view of the foregoing disclosure, it will be appreciated that any suitable number of types of immunological species (e.g. antibody), or types of imprinted materials, or any suitable combination of such immunological species (e.g. antibodies) and such imprinted materials, and any suitable number of types of sensor may be used depending upon the number of analyte species it is desired to detect and the type of sensor means it is desired to use. Thus, for example, a single type of analyte may be separated using a single type of immunological species (e.g. antibody), or a single type of imprinted material, and detected using a single discrete chemical sensor, or a single type of analyte may be separated using a single type of immunological species (e.g. antibody), or a single type of imprinted material, and detected using an array of sensors which array forms an olfactory sensor array. Conversely, a plurality of analyte species may be separated using a plurality of different types of immunological species (e.g. a plurality of different types of antibody), or a plurality of different types of imprinted material, or any suitable combination of such immunological species (e.g. antibodies) and materials, and detected sequentially using one type of single discrete chemical sensor means or by use of a plurality of different types of discrete chemical sensor means or by use of a plurality of chemical sensors comprising an olfactory sensor array.

It will be appreciated that, by way of example, when it is desired to seek to separate more than one analyte species from a sample, the selective separation means may include, for example, a plurality of different types of immunological species (e.g. antibody) appropriate to the analyte species that it is desired to separate from a sample. Thus, for example, the selective separation means may include an immunological species (e.g. an

antibody) of a first type, said immunological species (e.g. antibody) of a first type being appropriate for taking part in an immunological specific binding reaction with a given first analyte species, an immunological species (e.g. antibody) of a second type, said immunological species of a second type being appropriate for taking part in an immunological specific binding reaction with a given second analyte species and so forth, the number of different types of immunological species (e.g. types of antibody) used being dependent upon the number of different types of analyte species that it is desired to separate from a sample. A plurality of different immunological species types (e.g. antibody types) may be used in a manner such that said plurality of different immunological species types (e.g. antibody types) may be considered to provide a set or "panel" of immunological species types (e.g. a set or "panel" of antibody types).

It will also be appreciated that, by way of further example, as an alternative to using immunological species (e.g. antibodies) a plurality of different types of imprinted materials may be used when it is desired to seek separation of more than one analyte species from a sample; thus, for example, the selective separation means may include a plurality of different types of imprinted materials appropriate to the analyte species that it is desired to separate from a sample. Thus, for example, the selective separation means may include an imprinted material of a first type, said imprinted material of a first type being appropriate for undergoing selective interaction with a given first analyte species, an imprinted material of a second type, said imprinted material of a second type being appropriate for undergoing selective interaction with a given second analyte species and so forth, the number of different types of imprinted material being dependent upon the number of different types of analyte species that it is desired to separate from a sample. The plurality of

different imprinted material types may be used in a manner such that said plurality of different types of imprinted material may be considered to provide a set or panel of imprinted material types.

By way of yet further example, if desired, when it is desired to seek to separate more than one analyte species from a sample, the selective separation means may comprise any suitable combination of an immunological species type (e.g. antibody type) or immunological species types (e.g. antibody types) and an imprinted material type or a plurality of imprinted material types.

It is to be understood that the present invention may be used in the detection of more than one type of analyte species present at low concentrations in a sample.

Thus, where for example, the invention is to be utilised in seeking to detect the presence or absence of a plurality of different analyte species which it is thought may be present in the sample at inconveniently low levels (e.g. at levels which make detection difficult or impossible by use of known apparatus or methods), the apparatus, in accordance with the present invention, preferably includes a concentration means for concentrating each of a plurality of different types of analyte species and a method in accordance with the present invention preferably includes a concentration step for concentrating each of a plurality of different types of analyte species.

Thus, in accordance with yet a further embodiment of the present invention, there is provided apparatus, suitable for use in the detection of analyte species, which apparatus includes a selective separation means for separating each of a plurality of different types of analyte species from a sample, a concentration means for concentrating each of a plurality of different types of analyte species separated from a sample, and a sensor means, comprising a chemical sensor means, said chemical

sensor means being appropriate for detecting a plurality of different types of analyte species obtained from a sample and received from the selective separation means via the concentration means.

In accordance with the immediately preceding embodiment of the present invention, by way of example, if desired, a concentration means may be part of a selective separation means.

Also, in accordance with yet a further embodiment of the present invention, there is provided a method, which method is suitable for use in the detection of analyte species, which method includes separating each of a plurality of different types of analyte species, if present, from a sample by use of a selective separation means, concentrating any of each such separated different types of analyte species, and detecting each of any said different types of analyte species, if present, by use of a sensor means, comprising a chemical sensor means, said chemical sensor means being appropriate for detecting a plurality of different types of analyte species obtained from a sample and received from the selective separation means via a concentration step.

In accordance with the two immediately preceding embodiments of the present invention, by way of example, the chemical sensor means may be any suitable chemical sensor means such as those disclosed in accordance with the present invention; thus, for example, the chemical sensor means may be a single discrete chemical sensor means, or a plurality of discrete chemical sensor means, or a plurality of sensors in the form of an olfactory sensor array.

By way of further example, when utilising the present invention to detect a plurality of different types of analyte species, a plurality of different types of analyte species may, for example, be separated from a sample by means of a selective separation means which includes a plurality of different types of immunological

species (e.g. antibodies), such that each of said different types of analyte species may be separated from a sample and from each other, such that each of said different types of analyte species may be transferred separately (after any further processing, if desired, such as concentrating), to a discrete chemical sensor means capable of detecting said plurality of species, or to a plurality of different discrete sensor means, each of which discrete chemical sensor means is substantially specific for the type of analyte species transferred to it, or to a plurality of sensors in the form of an olfactory sensor array.

By way of yet further example, when utilising the present invention to detect a plurality of different types of analyte species, as disclosed in the immediately preceding paragraph hereinbefore, instead of using a plurality of different types of immunological species (e.g. antibodies), a plurality of different types of imprinted material may be used or any suitable combination of an immunological species type (e.g. antibody type) or plurality of immunological species types (e.g. antibody types) and an imprinted material type or a plurality of imprinted material types may be used.

In accordance with an embodiment of the present invention there is provided apparatus, suitable for use in the detection of a plurality of different analyte species, which apparatus includes a selective biological separation means, which selective biological separation means includes a plurality of different types of immunological species (e.g. antibody), a concentration means, which may optionally be part of the selective biological separation means, and a sensor means comprising a chemical sensor means, which chemical sensor means is an olfactory sensor array.

It will be appreciated that, by way of example, an immunological species type (e.g. an antibody type) or

immunological species types (e.g. antibody types), or an imprinted material type or imprinted material types, or any suitable combination of immunological species type (e.g. antibody type) or immunological species types (e.g. antibody types) or an imprinted material type or imprinted material types, may be used to "trap" an analyte species or a plurality of different analyte species from a sample.

It is to be understood that the present invention may find application in qualitative detection of an analyte species or of a plurality of analyte species, which also may be considered to be qualitative analysis, or in quantitative detection of an analyte species or a plurality of analyte species, which may be considered to be quantitative analysis (i.e. measurement or determination of an analyte species or a plurality of analyte species).

It will be appreciated that, for example, the present invention may also be used to indicate the absence of any analyte species (e.g. as in the case of a sample which contains no analyte species such as a "standard" containing no analyte species or a sample to be tested which contains no analyte species).

By way of example, if desired, in carrying out detection of an analyte species in accordance with the present invention, an authentic analyte species may be used, *inter alia*, as a calibrator or a standard. Where a plurality of analyte species are to be detected, a plurality of different authentic analyte species may be used as is appropriate. It is to be understood that an "authentic analyte species" is a species which is capable of reacting in a substantially similar manner as an analyte species to be detected under similar conditions.

The present invention may find application in detection of an analyte species or a plurality of different types of analyte species in any suitable sample. Thus, for example, any suitable fluid medium

(e.g. a liquid medium or a gaseous medium) may be used to provide a sample for use in accordance with the present invention.

By way of example, the apparatus of the present invention may include any suitable means for introducing a sample to the selective separation means. Thus, for example, a liquid sample may be introduced by means of a peristaltic pump.

Alternatively, by way of example, a gaseous sample or vapour sample may be used to provide a sample which is then applied to a selective separation means. Thus, for example, a gas sampling apparatus, or a vapour sampling apparatus, may be used to obtain a gaseous sample, or vapour sample, which gaseous sample, or a vapour sample, may then be investigated for analyte species. A gas sample, or a vapour sample, may, for example, be used to provide a liquid sample (e.g. by the addition of water or an aqueous reagent optionally in selected volumes) and said liquid sample may then be introduced to a selective separation means in accordance with the present invention. If appropriate, a sample may be formed, for example, by forming a vapour of an analyte species; thus, for example, a gas (e.g. nitrogen) may be passed through a liquid in order to generate a gas/vapour sample for application to the selective sensing means.

By way of further example, in some circumstances, a gaseous or vapour sample may be introduced to a selective separation means without forming a liquid sample therefrom. Thus, for example, where a selective separation means includes an immunological species (e.g. antibody) or immunological species (e.g. antibodies) it may be possible to maintain the immunological species (e.g. antibody) or immunological species (e.g. antibodies) wet with water or an aqueous medium and to apply a gaseous or vapour sample to the immunological species (e.g. antibody) or immunological species (e.g. antibodies) by flowing a sample past them.

Also, by way of example, in some circumstances, when using a selective separation means which includes an imprinted material of an appropriate type, it may be possible to introduce a gaseous or vapour sample without forming a liquid sample.

Any suitable gas sampling system, or vapour sampling system, may be used in accordance with the present invention; thus, for example, a high through-put air sampling apparatus (e.g. one capable of taking in a large volume of air) may be used in apparatus in accordance with the present invention. A filter may be used, if desired, to remove unwanted particulate material from a sample, prior to further processing.

The present invention may be applied, for example, to the detection of an analyte species or a plurality of different types of analyte species in, for example, mixtures of gases or vapours, in airborne mixtures, particulates (e.g. in a gaseous medium or vapour medium), liquids containing water-borne chemicals, and extracted mixtures of organic chemicals (e.g. in a liquid or gaseous phase).

By way of example, the present invention may be applied to the detection of airborne chemical species, airborne biological species, water pollutants (e.g. pesticides such as PCBs), biological species in clinical samples (e.g. in samples of blood, urine, breath and saliva), analyte species in food items (e.g. in fresh and processed foods, beverages, beers, spirits and foodstuffs' raw materials), fragrance-imparting species, flavour-imparting species, petrochemical materials, mal-odours, and bacteria. It will be appreciated that the present invention may find application, for example, in the detection of any suitable analyte species (e.g. any suitable hapten).

Where, by way of example, a single analyte species is to be separated from a sample, a single type of immunological species (e.g. a single type of antibody

species), or a single type of imprinted material, may be provided in the selective separation means such that said analyte species undergoes immunological specific binding interaction with said immunological species (e.g. - antibody species), or selective interaction with said imprinted material, such that the analyte species is selectively separated from the sample.

Where, by way of example, a plurality of different types of analyte species are to be separated from a sample, a plurality of different types of immunological species (e.g. a plurality of different types of antibody), or a plurality of different types of imprinted material, or any suitable combination of immunological species or immunological species (e.g. antibody or antibodies) and imprinted material or materials, may be provided in the selective separation means such that the various types of analyte species undergo specific binding interaction with immunological species (e.g. antibodies) or selective interaction with imprinted materials such that analyte species are each selectively separated from the sample.

It will be appreciated that an analyte species which is specifically bound by an immunological species (e.g. an antibody), or is selectively retained by an imprinted material, may be recovered from the selective separation means by any suitable means such as treatment with a suitable removal agent (e.g. elution with a suitable reagent or reagents). Any suitable removal agent or agents, or any suitable combination of such agents, may be used in the recovery of an analyte species or analyte species from an immunological species or immunological species (e.g. an antibody or antibodies), or from an imprinted material or imprinted materials. Examples of removal agents are heat pulse, solvent (or mixture of solvents such as a mixture of aqueous and organic solvents (e.g. say 80% ethanol solution with water)), and a suitable gas or air flow. Where, for example, a

solvent is used, the solvent may be used in liquid or vapour phase as may be appropriate. If desired, for example if an analyte species is present in a sample at an inconveniently low level for detection, the concentration of the analyte species may be increased, for example by removal into a limited volume of a suitable medium such as by elution into a limited volume of eluting medium. Thus, for example, apparatus in accordance with the present invention may include concentration means comprising means for removal (e.g. eluting) an analyte species or a plurality of different types of analyte species respectively into a selected limited volume or volumes of reagent or reagents. The concentration means may, if desired, be part of the selective separation means.

From the foregoing it will be appreciated that analyte species removed from an immunological species or immunological species (e.g. an antibody or antibodies), or imprinted material or imprinted materials, may be formed into a sample which is suitable for, or may be further treated to render it suitable for, introduction to a sensor means and in this Specification such a sample is identified as "a sensing sample". Such a sensing sample may be in any suitable form, or may be treated such as to be in a suitable form, for applying to a sensor. Thus means for generating a vapour phase sensing sample may be used such that a vapour phase sensing sample is formed for application to a suitable sensor means. Such a vapour phase sensing sample may be formed, for example, by heating a liquid sensing sample.

It is to be understood that, by way of example, where a chemical sensor means is such that a liquid sample may be applied to it (e.g. as may be the case with certain optical chemical sensors) then it may not be necessary to provide a vapour phase sensing sample.

Where, for example, more than one type of analyte species is to be recovered, it is to be understood that

by suitable recovery of different analyte species from an immunological species or immunological species (e.g. an antibody or antibodies), or from an imprinted material or imprinted materials, or any suitable combination thereof, of the selective separation system, a purified set of analyte species may be obtained (and concentrated if desired) such that a plurality of sensing samples may be prepared for introduction to a suitable sensor means. By way of example, one of said plurality of sensing samples may contain one of said analyte species, another of said plurality of sensing samples may contain another of said analyte species, and so forth, the number of sensing samples depending upon the number of different analyte species which it is desired to detect.

From the foregoing disclosure, it will be appreciated that any suitable chemical sensor means (as hereinbefore defined) may be used in accordance with the present invention.

Thus, for example, as hereinbefore disclosed, a piezoelectric sensor may be used in accordance with the present invention and said piezoelectric sensor may include, for example, an acoustic-electric transducer device. Thus an acoustic-electric transducer device may be used as a discrete chemical sensor or an array of such devices may be used as an olfactory sensor array.

By way of example, an acoustic-electric transducer device suitable for use in accordance with the present invention, may be an acoustic wave transducer device.

An example of one type of acoustic wave transducer device is a surface acoustic wave sensor. A surface acoustic wave sensor may be a delay-line device or a resonator device which may operate, for example, typically at fundamental frequencies in the range of 50-500 MHz.

Other examples of acoustic wave transducer devices which may find application in accordance with the present invention, are Love wave devices (LW), flexural plate

wave devices (FPW), acoustic plate mode devices (APM) and bulk acoustic wave resonators (BAW).

Acoustic wave transducer devices may be employed as a feedback element in an oscillator circuit and a measurement of frequency made. Alternatively, or additionally, direct measurement of acoustic wave velocity, phase or attenuation may be used as alternative response signals.

A response from a sensor or a response profile or response pattern from an olfactory sensor array may be analysed by mathematical techniques such as statistical methods (e.g. discriminant function analysis, principal component analysis and cluster analysis), techniques based on artificial neural networks, fuzzy logic or neuro-fuzzy methods. If desired in addition to steady-state or pseudo-steady-state sensor device responses, the kinetics of a sensor response and recovery (i.e. sensor dynamics) may be analysed in order to derive information relating to a sample.

An antibody or antibodies for use in accordance with the present invention may be prepared in any convenient manner such as those known in the art. Thus, for example, an antibody or antibodies for use in accordance with the present invention may be raised in animals in accordance with known procedures and may be further treated (e.g. purified) if desired.

Where a species is of a molecular weight which is too low to produce a satisfactory immunological response such that an antibody cannot be produced satisfactorily (as may be the case in relation to haptens), such species, or suitable derivatives thereof, may be coupled to a suitable carrier protein or carrier proteins in accordance with known procedures to produce high molecular weight complexes which can be used to raise suitable antibodies by procedures known in the art.

By way of example, reference may be made to UK Patent No. 2255637B which discloses, *inter alia*, antibody preparation.

The term "antibody" as used herein embraces whole antibody and antibody fragments such as Fab and $(Fab)_2$ and, accordingly, the term "antibodies" embraces whole antibodies and antibody fragments.

An antibody or antibodies in the selective separation means may be provided, in any suitable manner, on a suitable support material. By way of example, an antibody may be provided on a support material by being linked either directly or indirectly to a support material. An antibody may be linked to a support material by, for example, covalent linkage. By way of example, antibodies may be provided (e.g. as a coating) on spheres of suitable support material (e.g. spherical beads of, for example, 250-500 μ diameter) or a filament network.

Any suitable imprinted material may be used in a selective separation means in accordance with the present invention. Reference may be made to the literature relating to imprinted materials in this context. Thus, for example, reference may be made to "Molecular Imprinting" by Klaus Mosbach in TIBS 19 January 1994, pages 9-14.

An imprinted material or imprinted materials may be, for example, provided in a selective separation system in any suitable way on a suitable support material. Thus, for example, an imprinted material or imprinted materials may be linked in any convenient manner to a support material in a manner analogous to the provision of an antibody or antibodies on a support material as hereinbefore disclosed.

An immunological species comprising an antigenic ligand may be, for example, provided on a support material in any suitable manner such as by means of methods known in the art.

Examples of support materials which may find application in accordance with the present invention are solid phase materials such as a reaction vessel wall, insoluble polysaccharides, microparticles (e.g.

particulate microcellulose), polystyrene (e.g. in any suitable physical shape such as beads or discs), cross-linked dextran (e.g. Sephadex), insoluble polymer structures, glass surfaces, derivatised silica surfaces (e.g. having silyl groups with chemical functions attached), soluble polymers attached to a suitable surface (e.g. a glass surface), microparticulate materials with entrapped ferrous oxide (magnetisable particles), nylon and polyamides.

By way of example, the selective separation means may also act as a purification means inasmuch in that it may selectively remove an analyte species or a plurality of different types of analyte species from a sample, thereby to separate such species from other species which may be present in the sample. Thus, for example, other components of a medium from which a sample is taken may pass through the selective separation means with substantially only desired species being selectively retained. Thus, for example, contaminants or species which may interfere with detection may pass through the selected separation means and thus be substantially eliminated from any subsequent processes in accordance with the present invention. Selective removal from a sample may be carried out, for example, such as itself to provide "pre-concentration" of an analyte species or analyte species, before any other concentration which may optionally be effected.

By way of example, concentration of an analyte species or analyte species may be effected by a concentration means, which concentration means may, if desired, be part of the selective separation means.

By way of example, by selective removal of each of a plurality of different types of analyte species, each from its respective immunological species (e.g. antibody), or imprinted material, it is possible to obtain a plurality of sensing samples, each of which sensing samples contains substantially only one type of

analyte species; thus, if desired, each different type of analyte species may be introduced separately (e.g. sequentially) to a chemical sensor means.

Thus, for example, in accordance with the present invention, a plurality of different type of analyte species may be removed from a sample by means of immunological species (e.g. antibodies), imprinted materials or any suitable combination thereof, and released therefrom and delivered individually to a sensor means.

A particular immunological species (e.g. antibody) type or imprinted material type to be used in accordance with the present invention may be provided on a support material and the support material may be contained in a suitable container. Where it is desired to use more than one type of immunological species (e.g. more than one type of antibody), or more than one type of imprinted material type, or to use a combination of immunological species types (e.g. antibody or antibody types) and imprinted material or imprinted material types, in accordance with the present invention, a plurality of containers may be used; a first container may contain a first immunological species type (e.g. a first antibody type) or a first imprinted material type (e.g. provided on a support material such as particles), a second container may contain a second immunological species type (e.g. antibody type) or a second imprinted material type (e.g. provided on a support material such as particles), and so forth, depending on the number of immunological species types (e.g. the number of antibody types) or imprinted material types it is desired to utilise.

By way of example, the containers may be in any suitable form such as cartridge form, or any other suitable form, which may allow them to be stacked or packed together such that a sample may be passed through them.

By way of example a magazine comprising a plurality of cartridges may be utilised if desired; by way of example, one, some, or all of the cartridges in such a magazine may be replaced as desired, for example to retain detection efficiency at a desired level.

By way of example, it may be advantageous, if desired, for an apparatus, in accordance with the present invention, to be constructed in a modular manner. Thus, for example, an apparatus may include a first module which may comprise a sampling system for drawing a sample from any suitable source (e.g. from a suitable fluid medium (for example the environment)) and, if required, means for turning the sample into a form suitable for introduction to a second module which comprises a selective separation means (which includes an immunological species of a given type (e.g. an antibody of a given type) or a plurality of immunological species types (e.g. a plurality of types of antibodies), or an imprinted material of a given type, or a plurality of types of imprinted materials, or any suitable combination of immunological species type or immunological species types (e.g. antibody or antibody types) and imprinted material or imprinted material types) and, if required, means for concentrating analyte species, and means for transferring a sensing sample to a third module which comprises a sensor means.

Signal output from the third module may be fed to suitable data processing means and output from such data processing means may be fed to a suitable signal means which may comprise, for example, means for displaying analyte species concentration or concentrations or alarm means; it is to be understood that where the signal means is an alarm means, the signal means may be used to indicate the presence of an analyte species or analyte species, rather than to display concentration or concentrations of an analyte species or analyte species.

From the foregoing disclosure, it will be appreciated that a signal or signals from a sensor means in accordance with the present invention may be used, for example, to display an analyte concentration or analyte concentrations (e.g. in any suitable form such as numerical characters on an LCD display) or, for example, to give rise to an alarm signal.

By way of example, the present invention may be utilised to check for particular combinations of analyte species (e.g. molecules) or for analyte species levels exceeding given threshold levels or for the presence of a given type of analyte species.

The present invention may be, for example, utilised to detect an analyte species or analyte species which is/are present at ppb to ppt levels of concentration in a sample.

The selected separation means and the sensor means may be arranged, in accordance with the present invention, to be such that a response to an analyte species is, or that a responses to analyte species are, rapid. Thus, for example, it may be arranged that a medium is sampled for a few seconds (e.g. five seconds), separated and concentrated for a few seconds (e.g. five seconds), and then passed to a sensor means.

The selective separation means and the sensor means may be, for example, such that processes which take place therein are readily reversible so as to facilitate rapid re-use.

By way of example, it is to be understood that the chemical sensor means may be "tailored" to a particular analyte species or plurality of different types of analyte species for which it is desired to investigate a given sample. Thus, for example, a discrete chemical sensor means, or a plurality of discrete chemical sensor means, or an array of sensors in the form of an olfactory sensor array, may be arranged such as to "recognise" a

selected analyte species or a plurality of selected different types of analyte species.

From the foregoing disclosure it will be appreciated that the present invention may, for example, utilise highly specific bio-affinity separation and concentration, or highly specific imprinted material separation and concentration, in conjunction with selective chemical sensor detection (which may, for example, include the use of a sensor or sensors utilising a selective coating or coatings) so as to provide a "two-tier" selectivity.

Thus, for example, the present invention may offer the possibility of detecting an analyte species or a plurality of different types of analyte species with high specificity and high sensitivity.

The present invention may, for example, offer advantages over devices which comprise an immunological species (e.g. antibody), or an imprinted material, immobilised directly upon the surface of an acoustic-electric transducer. Thus, the present invention may be used to give better signal-to-noise ratios, better reversibility and better detection limits than devices having directly immobilised immunological species (e.g. antibodies).

Also, the present invention may offer, for example, advantages over immunoassay methods, which immunoassay methods may be unacceptably slow for certain detection requirements.

It will be appreciated that, by way of example, a chemical sensor means in accordance with the present invention may detect any suitable analyte species; thus, for example, a chemical sensor means may be such as to be capable of detecting chemical species as such or may be such as to be capable of detecting biological species.

The present invention may find application in, for example, simultaneous or sequential detection of a

plurality of different analyte species in complex mixtures.

By way of example, the present invention may find application in the simultaneous detection of say 2 to 20 different analyte species.

By way of example, an apparatus in accordance with the present invention may, if desired, be constructed so as to be readily transportable. Also, by way of example, an apparatus in accordance with the present invention may be constructed so as to be conveniently robust for field-use. For example, an apparatus in accordance with the present invention may, if desired, by constructed so as to be a portable, self-contained unit.

The present invention may, by way of example, be utilised, if desired, such that while one stage in a detection of an analyte species or analyte species is being carried out, another stage may be carried out on a later or earlier collected sample.

It is to be understood that, by way of example, apparatus in accordance with the present invention may, if desired, be used to take and process sequential samples from a suitable fluid medium (at any rate desired (e.g. at rapid frequency if desired)) to enable said medium to be monitored over a selected period.

By way of example, if it is desired to investigate a non-fluid material, such as a material in the solid state, for an analyte species or a plurality of types of analyte species, then such a material may be formed into a suitable fluid medium (e.g. by dissolution in a suitable solvent) for sampling.

Also, in accordance with the present invention, by way of example, it is to be understood that, if desired, analyte species from a first sample may be at the stage of being sensed, whilst a later second sample is at the stage of being subjected to separation and concentration, whilst an even later third sample is at the stage of being sampled.

By way of example, an apparatus in accordance with the present invention and suitable for use in sensing of an analyte species or a plurality of types of analyte species, may be considered, for example, to be a sensor apparatus.

It is to be understood that, in many applications, an analyte species will be an analyte species *per se*; however, it is also to be understood that in some circumstances an analyte species may be part of another species (e.g. part of a complex). Thus, the term "analyte species" as used herein embraces analyte species *per se*, and, as appropriate, species of which an analyte species is part.

It is to be understood that where, for example, a plurality of immunological species are used, the plurality may be all antibodies, all antigenic ligands or any suitable combination of antibody or antibodies and antigenic ligand or antigenic ligands.

The present invention will now be further described, by way of example only, with reference to the single Figure 1 of the accompanying Drawings which Figure 1 is a diagrammatic representation of an apparatus suitable for use in the detection of analyte species in accordance with the present invention.

Referring to the single Figure 1 of the accompanying Drawings, there is shown a representation of an apparatus 1 in accordance with the present invention, which apparatus 1 has a sampling means 2, a selective separation means 3, a sample transfer means 4, a sensor means 5, a data processing means 6 and a signal means 7.

The signal means 7 may be, for example, a display means for indicating the concentration of an analyte species or the concentrations of a plurality of analyte species or, for example, the signal means 7 may be an alarm means which is capable of indicating the presence of a given analyte species or a plurality of analyte species.

The sampling means 2 may include an intake means indicated by 2a and a means 2b for presenting a sample to the selective separation means 3.

Where a sample obtained by means of intake means 2a is not suitable for direct introduction to the selective separation means 3, means 2b may also include means for converting the sample into a sample for introduction to the selective separation means 3. Thus, for example, where a gaseous medium is to be investigated with respect to an analyte species or a plurality of analyte species, the intake means 2a may be, for example, any suitable intake means capable of introducing gaseous medium to the means 2b.

Where, for example, a gaseous medium is to be investigated with regard to an analyte species or a plurality of analyte species, the means 2b may include means for processing a gaseous medium such as to provide a liquid sample for introduction to the selective separation means 3. Thus, for example, the means 2b may include means for extracting an analyte species or a plurality of analyte species from a gaseous medium into a liquid medium.

The selective separation means 3 may include a suitable number of types of immunological species (e.g. types of antibody) and/or any suitable number of types of imprinted material. Thus, for example, the selective separation means 3 may include one type of immunological species (e.g. one type of antibody), or may include a plurality of types of immunological species (e.g. a plurality of types of antibody), or may include one type of imprinted material, or may include a plurality of types of imprinted materials, or may include one type of immunological species (e.g. one type of antibody) and one type of imprinted material, or one type of immunological species (e.g. one type of antibody) and a plurality of types of imprinted material, or may include a plurality of types of immunological species (e.g. a plurality of

types of antibody) and one type of imprinted material, or may include a plurality of types of immunological species (e.g. a plurality of types of antibodies) and a plurality of types of imprinted materials. An immunological species type (e.g. an antibody type), or a plurality of immunological species types (e.g. or a plurality of antibody types), or an imprinted material, or a plurality of imprinted materials, or any suitable combination of immunological species and imprinted material, may be provided on any suitable support material. Where, for example, the selective separation means 3 includes one type of immunological species (e.g. one type of antibody) or a plurality of types of immunological species (e.g. a plurality of types of antibody), then the separation means 3 may include means for removing an analyte species or a plurality of analyte species, which has or have been selectively removed from a sample obtained from sampling means 2 by means of specific binding interaction with one type of immunological species (e.g. one type of antibody), or with a plurality of types of immunological species (e.g. a plurality of types of antibody), from one type of immunological species (e.g. one type of antibody) or from a plurality of types of immunological species (e.g. a plurality of types of antibodies) such as to permit preparation of a sample or samples for introduction to the sample transfer means 4.

By way of further example, where the selective separation means 3 includes one type of imprinted material or a plurality of types of imprinted material, the selective separation means 3 may include means for removing an analyte species or plurality of analyte species, which has or have been selectively removed from a sample obtained from sampling means 2 by selective interaction with one type of imprinted material or with a plurality of types of imprinted material, from one type of imprinted material or from a plurality of types of imprinted materials, such as to permit preparation of a

sample or samples for introduction to the sample transfer means 4.

By way of further example, where a selective separation means 3 includes a combination of immunological species or immunological species (e.g. antibody or antibodies) and imprinted material or imprinted materials, the selective separation means 3 may include means for removing analyte species, or a plurality of analyte species, from an immunological species (e.g. an antibody) or immunological species (e.g. antibodies) or from an imprinted species, or a plurality of imprinted species, such as to permit preparation of a sample or samples for introduction to the sample transfer means 4.

Where an analyte species is, or a plurality of analyte species are, present in a sample to be investigated at an inconveniently low level for detection, then the selective separation means 3 may include means for increasing the concentration of an analyte species or plurality of analyte species.

The sample transfer means 4 includes means for providing a sensing sample suitable for introduction to the sensor means 5. Thus, for example, the sample transfer means 4 may include means for providing a sensing sample in a vapour or gaseous form suitable for introduction to the sensor means 5.

The sensor means 5 includes at least one chemical sensor means in accordance with the invention and, for example, may include one discrete chemical sensor, a plurality of discrete chemical sensors or an array of chemical sensors in the form of an olfactory sensor array.

The sensing means 5 may be such that a selected analyte species or plurality of selected analyte species may be detected thereby. Any suitable sensor in accordance with the present invention may be used in sensor means 5; an example of a suitable sensor means is

a piezoelectric sensor such as a surface acoustic wave transducer having associated therewith a material capable of interacting with an analyte species. In an example of the present invention, the sensor means 5 may be an olfactory sensor array.

The data processing means 6 may be any suitable means for processing the output of the sensor means 5 such as to produce a signal which can be utilised by signal means 7.

In operation, a sample of a medium which it is desired to investigate (for an analyte species or for a plurality of analyte species) is collected by sampling means 2 and is introduced (after any necessary processing as hereinbefore disclosed) to the selective separation means 3.

In the selective separation means 3, where, by way of example, the selective separation means 3 includes an immunological species (e.g. an antibody) or a plurality of immunological species (e.g. a plurality of types of antibody), an analyte species, if present, undergoes immunological specific binding interaction with an immunological species (e.g. an antibody) capable of undergoing specific binding with said analyte species, or in the case of a plurality of different analyte species, if present, different analyte species undergo immunological specific binding interaction with a plurality of different immunological species (e.g. a plurality of different antibodies) each of which immunological species (e.g. antibodies) is appropriate to a different given analyte species.

Where, by way of example, the selective separation means 3 includes an imprinted material, or a plurality of types of imprinted material, an analyte species, if present, undergoes selective interaction with an imprinted material capable of undergoing selective interaction with said analyte species, or in the case of a plurality of different analyte species, if present,

different analyte species undergo selective interaction with a plurality of different types of imprinted material, each of which types of imprinted material is appropriate to a different analyte species.

By way of further example, where a selective separation means 3 includes a combination of an immunological species (e.g. antibody) or immunological species (e.g. antibodies) and imprinted material or imprinted materials, it is to be understood that an essentially similar selective separation may take place.

Subsequently an analyte species is, or a plurality of analyte species are, recovered from the immunological species (e.g. antibody), or immunological species (e.g. antibodies), or imprinted species, or plurality or imprinted species, or any suitable combination thereof (as is appropriate to what the selective separation mean includes), concentrated if required, and then introduced to the sample transfer means 4 from which a sensing sample is then transferred to the sensor means 5.

The presence or absence and, if desired, the concentration of an analyte species, or a plurality of analyte species if appropriate, is sensed by a single discrete sensor or a plurality of discrete sensors, or an array of sensors forming an olfactory sensor array and output from the sensor means 5 is passed to data processing means 6 which then provides a signal which can be utilised by signal means 7, for example to display a concentration or concentrations or to operate as an alarm.

The present invention will now be further described, by way of example only, as follows.

Example 1

A glass column (length 70 mm; I.D. 5 mm) was filled with particles (approx. 150 microns diameter) of molecularly imprinted material prepared to be selective

for 2-methoxy-3-methyl-pyrazine. (2-methoxy-3-methyl-pyrazine is a volatile liquid used in perfumery.)

The particles of molecularly imprinted material were prepared by a conventional bulk synthetic method; reference may be made in this context to, for example, Muller *et al.*, Makromol. Chem. Rapid Commun., (1993), 14, 637.

An essentially similar column was filled with an equal quantity of particles of non-imprinted material for references purposes; particles of non-imprinted material were prepared in an essentially similar manner to the particles of molecularly imprinted material with the exception that during a relevant stage in preparation 2-methoxy-3-methyl-pyrazine was omitted.

To generate 2-methoxy-3-methyl-pyrazine vapour nitrogen (at 100 ml min^{-1}) was bubbled through liquid 2-methoxy-3-methyl-pyrazine contained in a dreschel bottle.

The vapour thus generated was passed through the column containing particles of molecularly imprinted materials for 20 minutes and vented to waste.

During the passage of vapour through the column, vapour was available to be absorbed by particles therein.

Subsequently vapour flow through the column was replaced by nitrogen (100 ml min^{-1}) and the resulting flow from the column was directed to a pair of chemical vapour sensor means housed in a stainless steel chamber.

An essentially similar procedure was also carried out separately using the column containing particles of non-imprinted materials.

The sensor means were based on 10 MHz quartz crystal bulk acoustic wave resonators having gold electrodes; on surfaces of the electrodes a thin layer of polymeric coating material had been applied that was capable of absorbing, non-specifically, 2-methoxy-3-methyl-pyrazine.

The polymeric coating material used in one of the sensor means (designated here as Sensor 1) was a commercially available polysiloxane and the polymeric

coating material used in the other sensor means (designated here as Sensor 2) was a commercially available cellulose derivative.

It was observed that absorption of 2-methoxy-3-methyl-pyrazine led to a decrease in the frequency of oscillation of the Sensors 1 and 2.

For Sensor 1 the flow from the column containing particles of molecularly imprinted material gave rise to a frequency change (Hz) of 93, whereas the flow from the column containing particles of non-imprinted material gave rise to a frequency change (Hz) of only 10.

For Sensor 2 the flow from the column containing particles of molecularly imprinted material gave rise to a frequency charge (Hz) of 193, whereas the flow from the column containing particles of non-imprinted material gave rise to a frequency change (Hz) of only 28.

Thus, it may be seen that the particles of molecularly imprinted material were able to absorb 2-methoxy-3-methyl-pyrazine in a selective separation step and release it for detection by the sensor means.

Examples 2 to 6

These Examples are comparative Examples and relate to cross-reactivity of pyrazine derivatives other than that of Example 1 with the molecularly imprinted material of Example 1.

The same molecularly imprinted material and the same non-imprinted material as Example 1 were used.

Cross reactivities for various pyrazine derivatives were calculated as follows:

$$Cross\ Reactivity = \frac{A - B}{C - D} \times 100\%$$

where A = response to pyrazine derivative for flow from column containing molecularly imprinted material;

B = response to pyrazine derivative for flow from column containing non-imprinted material;

C = response to 2-methoxy-3-methyl-pyrazine for flow from column containing molecularly imprinted material; and

D = response to 2-methoxy-3-methyl-pyrazine for flow from column containing non-imprinted material.

Example 2

The procedure of Example 1 was followed with the exception that 2-ethyl-3-methyl-pyrazine was introduced to the columns rather than 2-methoxy-3-methyl-pyrazine.

The Cross Reactivity, calculated as hereinbefore disclosed, was 80%.

Example 3

The procedure of Example 1 was followed with the exception that 2,3-diethyl-pyrazine was introduced to the columns rather than 2-methoxy-3-methyl-pyrazine.

The Cross Reactivity, calculated as hereinbefore disclosed, was 25%.

Example 4

The procedure of Example 1 was followed with the exception that 2,5-dimethyl-3-ethyl-pyrazine was introduced to the columns rather than 2-methoxy-3-methyl-pyrazine.

The Cross Reactivity, calculated as hereinbefore disclosed, was 25%.

Example 5

The procedure of Example 1 was followed with the exception that 2-methoxy-3-isobutyl-pyrazine was introduced to the columns rather than 2-methoxy-3-methyl-pyrazine.

The Cross Reactivity, calculated as hereinbefore disclosed, was 15%.

Example 6

The procedure of Example 1 was followed with the exception that 2,3,5-trimethyl-pyrazine was introduced to the columns rather than 2-methoxy-3-methyl-pyrazine.

The Cross Reactivity, calculated as hereinbefore disclosed, was 13%.

Apparatus in accordance with the invention as mentioned above may comprise a portable self contained unit and advantageously it is hand-held. Furthermore, a combination of technology types may be used in the chemical sensor means, for example, it may include a metal oxide sensor and a conducting polymer sensor and an acoustic wave transducer in a single unit.

Claims

1. Apparatus, suitable for use in the detection of analyte species, which apparatus includes a selective separation means (as hereinbefore defined), for separation of an analyte species from a sample, and sensor means, comprising a chemical sensor means (as hereinbefore defined), for detecting analyte species received from the selective separation means.

2. A method, which method is suitable for use in the detection of analyte species, which method includes separating an analyte species, if present, from a sample by use of a selective separation means (as hereinbefore defined), and detecting the analyte species, if present, by use of a sensor means, comprising a chemical sensor means (as hereinbefore defined), for detecting analyte species received from the selective separation means.

3. Apparatus as claimed in Claim 1 wherein the apparatus includes means for concentrating an analyte species.

4. A method as claimed in Claim 2 wherein the method includes concentrating an analyte species.

5. Apparatus as claimed in Claims 1 or 3 or a method as claimed in Claims 2 or 4 wherein the selective separation means includes an immunological species capable of taking part in immunological specific binding reaction with the analyte species.

6. Apparatus or a method as claimed in Claim 5 wherein the immunological species is an antibody of a type which is capable of undergoing specific binding with the analyte species.

7. Apparatus or a method as claimed in Claim 5 wherein the selective separation means includes an antigenic ligand capable of taking part in immunological specific binding reaction with the analyte species.

8. Apparatus as claimed in Claims 1 or 3 or a method as claimed in Claims 2 or 4 wherein the selective separation

means includes an imprinted material of a type which is capable of undergoing selective interaction with the analyte species.

9. Apparatus as claimed in Claim 1, suitable for use in the detection of analyte species, which apparatus includes a selective separation means, for separating each of a plurality of different types of analyte species from a sample, and sensor means, comprising a chemical sensor means, said sensor means being appropriate for detection of a plurality of different types of analyte species obtained from a sample and received from the selective separation means.

10. A method as claimed in Claim 2, suitable for use in the detection of analyte species, which method includes separating a plurality of different types of analyte species, if present, from a sample using a selective separation means for separating each of a plurality of different types of analyte species from a sample, and detecting each of the different types of analyte species, if present, by means of a sensor means comprising a chemical sensor means, said sensor means being appropriate for detecting a plurality of different types of analyte species obtained from a sample and received from the selective sensor means.

11. Apparatus as claimed in Claim 9 wherein the apparatus includes means for concentrating each of a plurality of different types of analyte species.

12. A method as claimed in Claim 10 wherein the method includes concentrating any of each of separated different types of analyte species.

13. Apparatus as claimed in Claims 9 or 11 or a method as claimed in Claims 8 or 10 wherein the selective separation means includes a plurality of different types of immunological species, or a plurality of different types of imprinted material, or one type of immunological species and one type of imprinted material, or one type of immunological species and a plurality of types of

imprinted material, or a plurality of types of immunological species and one type of imprinted material, or a plurality of types of immunological species and a plurality of types of imprinted material.

14. Apparatus or a method as claimed in Claim 13 wherein the immunological species is an antibody or the plurality of types of immunological species is a plurality of types of antibody.

15. Apparatus or a method as claimed in any one of the preceding claims wherein the chemical sensor means comprises a discrete chemical sensor means.

16. Apparatus or a method as claimed in any one of Claims 1 to 14 wherein the chemical sensor means comprises a plurality of discrete chemical sensor means.

17. Apparatus or a method as claimed in any one of Claims 1 to 14 wherein the chemical sensor means comprises an olfactory sensor array.

18. Apparatus or a method as claimed in any one of Claims 15 to 17 wherein a chemical sensor means includes a piezoelectric sensor comprising an acoustic wave transducer.

19. Apparatus or a method as claimed in Claim 15 or Claim 16 wherein a chemical sensor means includes a metal oxide sensor, a conducting polymer sensor, or an optical sensor, or a catalytic sensor.

20. Apparatus or a method as claimed in Claim 18 wherein the acoustic wave transducer is a surface wave device.

21. Apparatus or a method as claimed in Claim 18 wherein the acoustic wave transducer is a bulk wave device.

22. Apparatus or a method as claimed in any one of the preceding Claims wherein a chemical sensor means has a surface which has a coating or a film of a material which is capable of interacting non-selectively with an analyte species.

23. Apparatus or a method as claimed in any one of Claims 1 to 20 wherein a chemical sensor means has a surface which has a coating or a film of a material which

is capable of interacting selectively with an analyte species.

24. Apparatus, suitable for use in the detection of a plurality of different analyte species, which apparatus includes a selective biological separation means, which selective biological separation means includes a plurality of different types of antibody, a concentration means, which may optionally be part of the selective biological separation means, and a sensor means comprising a chemical sensor means (as hereinbefore defined), which chemical sensor means is an olfactory sensor array.

25. Apparatus as claimed in Claim 24 wherein the olfactory sensor array includes a plurality of surface acoustic wave devices.

26. Apparatus or a method as claimed in any one of the preceding Claims wherein the apparatus or method is such as to permit detection of air-borne chemical species, an air-borne biological species, a water pollutant, a biological species from a clinical sample, an analyte species in a food item, a fragrance-imprinting species, a flavour-imparting species, a petrochemical species, a malodour or bacterium.

27. Apparatus as claimed in any preceding claim and adapted to be portable.

28. Apparatus as claimed in claim 27 and adapted to be suitable for hand-held use.

29. Apparatus as claimed in any preceding claim wherein the chemical sensor means includes more than one technology type of sensor.

30. Apparatus substantially as hereinbefore described with reference to the single Figure 1 of the accompanying Drawings.

31. Apparatus substantially as hereinbefore described with reference to Example 1.

32. A method, suitable for the detection of analyte species, substantially as hereinbefore described with reference to Example 1.

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Application No: GB 9828007.6
Claims searched: 1-32
Examiner: Dave Mobbs
Date of search: 4 March 1999

Patents Act 1977
Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.Q): G1N NBMA

Int Cl (Ed.6): G01N 33/543.

Other: ONLINE: EPODOC, JAPIO, WPI.

Documents considered to be relevant:

Category	Identity of document and relevant passage		Relevant to claims
Y	WO 97/45721 A	(Novartis AG) - see claim 1.	1-5 at least
X	WO 97/25619 A	(The Secretary of the US Navy)	1-4, 6 at least
Y	WO 97/09068 A	(University of Washington)	1-6 at least
Y	WO 96/33412 A	(Perspective Biosystems)	1-5 at least
X	WO 96/26435 A	(Thomson-CSF)	1-4, 8, 18 at least
X, Y	WO 93/25910 A	(Pharmacia Biosensor AB)	1-5 at least
X	WO 92/18867 A	(Amersham International Plc)	1-4, 6, 19 at least
X, Y	US 5,622,872	(Biocircuits Corporation)	1-5 at least
X, Y	US 5,252,493	(Nippon Telegraph and Telephone Corporation)	1-4, 6 at least
X, Y	US 5,082,630	(United States Department of Energy)	1-4, 6, 19 at least

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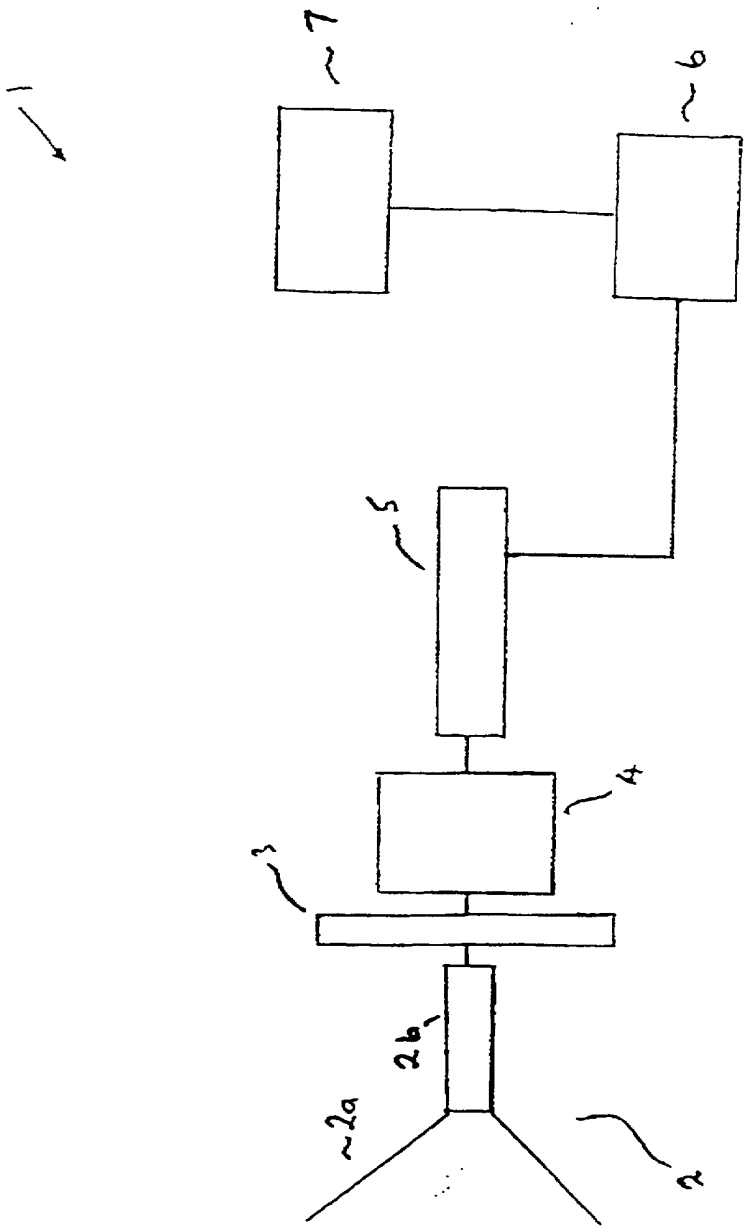

Fig 1